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THYMECTOMY IN TREATMENT OF MYASTHENIA GRAVIS

Report Based on Thirty-Two Cases

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INTEREST in the thymus gland as it relates to myasthenia gravis began in 1901, with Weigert's [1] report of a thymic tumor observed at necropsy in a patient who had died of myasthenia gravis. Pathologists, notably Bell,[2] Norris [3] and Miller,[4] became actively interested in the subject and were able to find thymic abnormalities in such a high proportion — approximately 50 per cent — of patients who died of myasthenia gravis that some sort of relation of the disease to the thymus gland became established. One of us (Eaton) has previously summarized the evidence for this relation.[5] The surgeons did not await the final solution of the problem before attempting to cure patients by removal of the thymus gland. The first surgical efforts, made before satisfactory medical treatment was available, and before the technic of thoracic surgery had advanced to its present status, were failures. With the report of Blalock, Mason, Morgan and Riven [6]

From the Department of Neurology and Psychiatry (Dr. Eaton), the Division of Surgery (Dr. Clagett), the Section on Roentgenology (Dr. Good) and the Section on Surgical Pathology (Dr. McDonald), the Mayo Clinic.

1. Weigert, C.: Pathologisch-anatomischer Beitrag zur Erb'schen Krankheit (Myasthenia gravis), Neurol. Centralbl. **20**:597-601 (July 1) 1901.

2. Bell, E. T.: Tumors of the Thymus in Myasthenia Gravis, J. Nerv. & Ment. Dis. **45**:130-143 (Feb.) 1917.

3. Norris, E. H.: The Thymoma and Thymic Hyperplasia in Myasthenia Gravis with Observations on the General Pathology, Am. J. Cancer **27**:421-433 (July) 1936; A Thymoma (Adenoma of the Thymus) from an Unusual Case of Myasthenia Gravis, with Observations on the General Pathology, ibid. **30**: 308-317 (June) 1937.

4. Miller, H. G.: Myasthenia Gravis and the Thymus Gland, Arch. Path. **29**:212-219 (Feb.) 1940.

5. Eaton, L. M.: Myasthenia Gravis: Its Treatment and Relation to the Thymus, Proc. Staff Meet., Mayo Clin. **17**:81-87 (Feb. 11) 1942.

6. Blalock, A.; Mason, M. F.; Morgan, H. J., and Riven, S. S.: Myasthenia Gravis and Tumors of Thymic Region: Report of a Case in Which the Tumor Was Removed, Ann. Surg. **110**:544-561 (Oct.) 1939

in 1939 of apparent success in the treatment of myasthenia gravis by removal of a tumor from the anterior part of the mediastinum, which tumor, although not histologically verified, was almost certainly of thymic origin, our interest, and that of other investigators, was aroused. After hearing the report by Campbell, Fradkin and Lipetz [7] at the meeting of the American Neurological Association in 1941, our colleagues in the department of neurology and we decided to study intensely the problem of myasthenia gravis and its relation to the thymus gland. We were soon rewarded with roentgenologic evidence of a large tumor in the mediastinum of a patient who had myasthenia gravis. Remission of the disease took place after roentgen irradiation of the tumor, and on Dec. 20, 1941 the tumor was removed surgically by one of us (Clagett). The thymic origin of the tumor was verified histologically.

One of the first problems confronting us was raised by the discrepancy between the frequency with which tumors of the thymus gland have been observed at necropsy and the infrequency with which they are found clinically. The great majority of patients with myasthenia gravis who have been seen at the Mayo Clinic throughout the years had had stereoscopic roentgenograms of the thorax made in the ordinary posteroanterior position. In spite of the large number of myasthenic patients who had undergone this type of examination, we were unable to find in previous records a single instance in which the diagnosis of thymic tumor was unequivocal. It is true that abnormal shadows in the anterior part of the mediastinum had been detected at infrequent intervals, and that clinicians had suspected that they were cast by tumors of the thymus gland; but the roentgenologists had been unable to attribute them definitely to the thymus gland. Apparently, the inability of roentgenologists to diagnose tumors of the thymus gland in patients with myasthenia gravis was not peculiar to this clinic. Viets and Schwab,[8] in a report of 50 cases of myasthenia gravis, stated: "We have been unable to associate myasthenia gravis with enlargement of the thymus gland. All roentgen ray studies were negative for enlargement of the gland." Viets, in discussing a paper by Campbell, Fradkin and Lipetz [7] in 1941, reported roentgenographic evidence of thymic tumor in only 1 of 85 cases.

In 1941 one of us (Good [9]) became interested in the roentgenologic aspects of the problem and undertook a study of the cases of myasthenia

7. Campbell, E.; Fradkin, N., and Lipetz, B.: Myasthenia Gravis Treated by Removal of Thymic Tumor: Report of Two Cases, Tr. Am. Neurol. A., 1941, pp. 14-15.

8. Viets, H. R., and Schwab, R. S.: Myasthenia Gravis: Clinical Observations of Fifty Cases, Compt. rend. internat. Cong. de neurol., Copenhagen **3**:21-25 (Aug.) 1939.

9. Good, C. A.: Roentgenologic Findings in Myasthenia Gravis Associated with Thymic Tumors, Am. J. Roentgenol. **57**:305-312 (March) 1947.

gravis at this clinic. In a study of 206 consecutive cases of myasthenia gravis, a diagnosis of thymic tumor was made by roentgenologic methods in 33. The accuracy of the roentgenologic diagnosis was verified surgically in 20 cases and at necropsy in 4 cases. In only 1 of this series of 33 cases did operation fail to verify the presence of a thymic tumor. In the remaining 8 cases the roentgenologic evidence of a mass in the anterior part of the mediastinum was unequivocal, but the opportunity for verification at operation or necropsy has not arisen.

No single type of roentgenologic examination was responsible for the diagnosis of thymoma in the 33 cases in which a tumor was found. Although posteroanterior roentgenograms of the thorax were made in every case, there were 14 instances in which the tumor could not be seen with this method. The diagnosis was made by means of roentgenoscopy in 9 of these cases and by means of a lateral roentgenogram in the remaining 5 cases. In 4 of the 33 cases roentgenoscopy afforded the only means of diagnosis, there being no evidence of a tumor in either the posteroanterior or the lateral roentgenograms.

Because of the difficulty experienced in recognition of the tumors in some cases in this series, it is now our custom to examine every patient with myasthenia gravis by means of roentgenoscopy, as well as to obtain a posteroanterior and a lateral roentgenogram of the thorax in each instance. Care is taken during roentgenoscopy to study the mediastinal structures with the patient in all positions. Any abnormal shadow is noted, and roentgenograms are made with the patient in such positions as will show the shadow to best advantage. It is especially important that the anterolateral borders of the mediastinal shadow be watched carefully while the patient is turned slowly to each side. In many cases the tumor can be seen first as a convex shadow along the margin of the normal shadow of the cardiovascular structures. Frequently, such a tumor is somewhat flat and is in close apposition to the pericardium. In such a case the tumor may exhibit a transmitted pulsation, which is difficult to distinguish from the pulsation of normal cardiovascular structures.

The position of the tumors in the anterior part of the mediastinum varied in this series of cases. For the most part, the tumors were found in the upper part of the anterior portion of the mediastinum, overlying the aortic arch and the base of the heart. It should be emphasized, however, that a thymic tumor may be situated lower in the thorax. In at least 3 instances the tumor was situated as low as the level of the ninth thoracic vertebra.

Sufficient calcium may be deposited in a thymoma to be apparent roentgenographically. In 2 of the cases in our series the calcium was observed in the wall of a cyst within the tumor; in another case it was distributed unevenly throughout the body of the tumor.

It is more difficult for the roentgenologist to find a tumor of the anterior part of the mediastinum in a patient with myasthenia gravis than it is to identify the type of tumor once it has been found. All the tumors in our series of cases originated in the thymus gland. It is conceivable that some other type of mediastinal tumor might develop in a patient with myasthenia gravis, but the possibility of such a coincidence must be slight.

Of the 173 cases in which roentgenologic evidence of thymic tumor was lacking, surgical exploration was made in 25, and the thymus was studied at necropsy in 3; in no case was a thymic tumor seen.

Thus, one may conclude that careful roentgenologic examination will reveal evidence of thymic tumor in approximately 15 per cent of cases of myasthenia gravis, i. e., in 32 of a series of 206. There is reason to believe that this percentage approaches the actual frequency of occurrence of thymic tumor among patients who have myasthenia gravis. The incidence of thymic tumor observed at necropsy in the reported cases of myasthenia gravis is higher, and probably less accurate, than the incidence established by roentgenologic examination, since there has been a tendency to report those cases in which a tumor was actually seen. Miller,[4] in 1940, summarized the literature as it pertains to the incidence of thymic abnormality observed at necropsy in cases of myasthenia gravis since Weigert's original report and added his own cases. Of a total of 87 cases, a thymic tumor was present in 20 and an abnormally large thymus gland in 21. Poer,[10] in 1942, stated that of 129 cases of myasthenia gravis in which necropsy or surgical exploration of the mediastinum was carried out, thymic tumor had been found in a total of 41, an incidence of 31.8 per cent.

Our experience would lead us to believe that the true incidence of thymic tumor among patients with myasthenia gravis is much less, probably not significantly greater than the incidence of 15.5 per cent detected by our roentgenologists. That necropsy reports may be misleading is attested to by our records. Seventeen complete necropsy studies in cases of myasthenia gravis have been made at the Mayo Clinic. Thymic tumor was present in 9 cases; but in 2 cases necropsy had been performed on patients who died subsequent to removal of the tumor, and in at least 3 other cases the patients came to us in a critical condition for consideration of surgical removal of a tumor of the thymus gland which had been found to be present by previous roentgenologic examination. Thus, the incidence of thymic tumor at necropsy is much higher in our series than would normally be true.

10. Poer, D. H.: Effect of Removal of Malignant Thymic Tumor in a Case of Myasthenia Gravis, Ann. Surg. **115**:586-593 (April) 1942.

TABLE 1.—*Clinical Data on Group 1: 15 Cases of Thymoma with Thymectomy*

TABLE 1.—*Clinical Data on Group 1: 15 Cases of Thymoma with Thymectomy*

Case No.	Age	Sex	Duration of Symptoms at Time of Operation	Period of Treatment with Neostigmine, at Time of Operation	Operation: Date	Operation: Approach: Sternum Split	Operation: Approach: Cartilage Resected	Operation: Approach: Rib Resected	Roentgen Therapy: Before Operation	Roentgen Therapy: After Operation	Period of Observation of Patient After Operation	Comment
						Patient Died Since Operation						
1	40	F	19 mo.	1 wk.	4/ 2/43	+	—	—	—	—	3 days	Tumor invaded surrounding structures; patient died suddenly of respiratory failure; necropsy not remarkable; roentgenographic evidence of tumor before onset of myasthenia gravis
						No Improvement						
2	40	F	13 yr.	1 yr.	10/23/43	—	+	—	—	+	2 yr. 5 mo.	Patient less well since operation
3	40	M	10+ mo.	6 mo.	5/ 7/42	—	+	—	+	+	3 yr. 3 mo.	Roentgenographic evidence of tumor over 1 year before onset of myasthenia; partial remission after roentgen therapy preceding operation
4	38	M	13 mo.	2½ mo.	7/11/44	+	—	—	+	—	10 mo.	Inoperable tumor; thoracic pain as symptom of tumor preceding onset of myasthenic symptoms 5 or 6 years
						Moderate Improvement						
5	57	M	1 yr. 10 mo.	5 mo.	10/24/42	—	—	+	+	+	3½ yr.	
6	41	M	2+ yr.	4+ mo.	3/16/43	—	—	+	+	+	1 yr. 7 mo.	Inoperable tumor; neoplastic implants on lung; improvement attributed to intensive roentgen therapy before and after operation
7	55	M	2 yr.	None	9/ 3/43	+	—	—	—	+	2 yr. 8 mo.	Tumor inoperable, invaded innominate vein and superior vena cava; improvement attributed to roentgen therapy after operation
8	32	M	2½ yr.	1 yr. (None for 1 yr. before operation)	6/11/43	+	—	—	+	—	1 yr. 8 mo.	Partial remission after roentgen therapy given 1 year before operation
						Considerable Improvement						
9	26	F	2+ yr.	10 mo.	8/17/42	—	—	+	+	+	3 yr. 5 mo.	Pain in the thorax, which may have been due to tumor, preceded onset of myasthenia gravis; intensive roentgen therapy before operation reduced size of tumor and seemed to produce remission of myasthenia gravis
10	45	M	1½ mo.	1 mo.	12/17/43	—	+	—	—	+	1 yr. 4 mo.	
11	47	M	2+ yr.	5 mo.	5/ 9/44	+	—	—	—	—	2 yr.	Hyperplastic thymus gland also resected
12	36	M	1 yr. 9 mo.	1 yr. 7 mo.	9/ 8/44	+	—	—	+	+	1½ yr.	Invasive tumor; all tissue removed except piece in neck and another attached to vein
13	55	M	6 mo.	5 mo.	12/20/41	—	+	—	+	—	4½ yr.	Almost complete remission after roentgen therapy 4 mo. before operation; complete remission after operation
14	41	M	6 mo.	1 wk.	12/21/42	+	—	—	—	+	1 yr. 3 mo.	Tumor and thymus gland removed; remission complete, or almost so
15	42	F	9 yr.	5 wk.	10/ 6/44	—	—	+	+	+	1 yr. 4 mo.	Lung invaded by tumor; complete remission after operation

Last, the 15.5 per cent incidence of tumors of the thymus gland, as demonstrated roentgenologically in our series of 206 cases of myasthenia gravis, agrees well with the 13.9 per cent incidence of tumors of the gland observed during thymectomy in 86 cases from the literature (Blalock,[11] 2 tumors in 20 cases; Viets,[12] 4 tumors in 15 cases; Keynes,[13] 6 tumors in 51 cases), in which no attempt was made at selection on the basis of roentgenologic evidence of thymic tumor.

TABLE 2.—*Clinical Data in Group 2: 17 Cases of Thymectomy But No Thymoma*

Case No.	Age	Sex	Duration of Symptoms at Time of Operation	Period of Treatment with Neostigmine Before Operation	Date of Operation	Period Patient's Condition Was Followed After Operation	Roentgen Treatment Before Operation	Comment
					Died Since Operation			
16	67	M	3+ yr.	2+ yr.	12/26/44	3 days	—	Patient died of respiratory failure; should have had benefit of artificial respirator
17	26	F	3 yr. 10 mo.	1 yr. 10 mo.	8/29/44	6 mo.	—	Patient died of respiratory failure; probably was improving when acute febrile illness supervened
18	40	F	3 mo.	2½ mo.	5/29/45	3 mo.	—	Progressive course not altered perceptibly by thymectomy
					No Improvement			
19	52	M	2 yr.	1 yr. 4 mo.	7/18/44	1 yr. 9 mo.	—	Insignificant amount of thymus gland found at operation
20	30	F	11 mo.	3 wk.	11/10/44	1 yr. 5 mo.	—	Subjective improvement
21	24*	F	4½ yr.	3 yr.	8/14/45	7½ mo.	+	No remission after roentgen therapy, 3 yr. before operation
22	22	M	3+ yr.	7 mo.	8/17/45	7½ mo.	—	
23	16†	F	3+ yr.	2 yr. 10 mo.	8/21/45	6 mo.	+	No improvement after roentgen therapy, 2½ yr. before operation
24	24	F	5½ yr.	5 yr. 4 mo.	9/ 7/45	6 mo.	+	Partial temporary remission after roentgen therapy, 2 yr. before operation
					Moderate Improvement			
25	52	F	7 yr.	2— yr.	1/18/43	3 yr. 3 mo.	+	
26	30	F	9 yr.	8 yr.	6/13/44	1 yr. 10 mo.	—	
27	22	F	2 yr. 5 mo.	1 yr. 9 mo.	11/17/44	1 yr. 4 mo.	—	
28	43	M	10+ mo.	7 mo.	5/29/45	11 mo.	—	
29	18	F	5 yr.(?), 1 yr. at least	1 wk.	6/ 1/45	9½ mo.	—	
					Considerable Improvement			
30	17	F	1+ yr.	9 mo.	9/ 7/45	7 mo.	—	
31	23	M	6 yr.	6 mo.	9/15/44	1 yr. 5 mo.	+	Ten roentgen treatments elsewhere, begun in April 1944
32	27	F	3 yr.	11 mo.	8/29/44	1 yr. 4 mo.	—	

* Patient was 21 years old when first seen and 24 years old at operation.
† Patient was 13 years old when first seen and 16 years old at operation.

Although the thymus gland was removed surgically in 46 of our series of 206 cases of myasthenia gravis, we shall confine the analysis

11. Blalock, A.: Thymectomy in the Treatment of Myasthenia Gravis: Report of Twenty Cases, J. Thoracic Surg. **13**:316-336 (Aug.) 1944.

12. Viets, H. R.: Myasthenia Gravis, J. A. M. A. **127**:1089-1096 (April 28) 1945.

13. Keynes, G.: The Surgery of the Thymus Gland, Brit. J. Surg. **33**:201-214 (Jan.) 1946.

of results to the 32 cases in which operation was performed between Dec. 20, 1941 and Sept. 7, 1945. Thus, there are included only cases in which the condition had been followed for at least six months on June 1, 1946, when the data regarding the results were assembled.

The most pertinent clinical data regarding the cases in this study are presented in tables 1 and 2. For more detailed information, the reader is referred to the reports of 10 of the 32 cases.

EVALUATION OF RESULTS

Despite experience gained from a specific interest in myasthenia gravis and in caring for many myasthenic patients, we are unable to predict with certainty the course of the disease in any particular case. Of course, predictions can be made roughly; but their accuracy is so limited that one cannot say that a particular patient who has had a pronounced remission of his symptoms of myasthenia gravis after thymectomy might not have experienced the remission spontaneously.

That difficulty in evaluation of results has been encountered should surprise no one familiar with the variable course of myasthenia gravis. The course may be particularly mild. Recently, we examined a patient who had had definite symptoms of myasthenia gravis continuously for twenty-two years, but to whom no specific treatment had been administered because the diagnosis of myasthenia gravis had not previously been made. During that period there had been the usual waxing and waning in the degree of severity of the disease, but no clearcut remission had occurred. The disease was becoming severer very gradually. This case is not unique. Dr. F. P. Moersch, of the Mayo Clinic, established the diagnosis of myasthenia gravis in a case in which the disease had been present for twenty-five years.

In addition to patients who have had the disease to a mild degree for many years, there are patients who experience remissions of varying degrees, sometimes complete, of many years' duration. The late Dr. Peter Bassoe wrote to one of us (Eaton) concerning a patient whom he had examined during a recurrence of myasthenia gravis after a period of twenty-nine years, during which time the symptoms had been entirely absent. One of our patients showed no signs of myasthenia gravis, even after the administration of quinine and solution of curare. Yet the history of the illness he had had for three years, more than twenty years earlier, was typical of myasthenia gravis and the disease had been diagnosed as such by a prominent neurologist elsewhere. We are convinced that this case represents a complete remission for many years, and possibly a spontaneous cure of myasthenia gravis.

In another case of interest from the standpoint of variability of the course, a man aged 19 had had an average of one attack of severe myasthenic weakness, lasting from two to four weeks, every year since

the age of 11. Although he presented severe weakness at the time we examined him, he said that his remissions had been complete. The fact that he was later inducted into the Army would seem to substantiate his statement.

At present we have little statistical information regarding the frequency of remissions in our cases of myasthenia gravis. From a study of 100 consecutive cases, we learned that a definite remission, in contrast to the usual minor variation in symptoms, had occurred in 24 cases before the patients came to us for examination.

We are not attempting to make a case for the benignity of myasthenia gravis; rather, we are trying to emphasize that the course of myasthenia gravis is at times much less serious than would be inferred from much of the medical literature. On the other hand, myasthenia gravis is often a serious disease. Almost half our patients must seriously restrict their work and recreational activities in spite of adequate treatment with neostigmine and ephedrine and occasional supplements of guanidine hydrochloride and a potassium salt. Furthermore, 12 per cent of our patients are known to have died within two years after their initial visit to this clinic. This realization that the course of myasthenia gravis is extremely variable has forced us to conclude that the results in this group of 32 cases do not furnish conclusive evidence as to the value of thymectomy in the treatment of this disease. Despite this, we trust that a report at this time will be useful in indicating an apparent trend in the response of myasthenic patients to thymectomy and in presenting knowledge gleaned from operative and postoperative experience with these patients and from pathologic study of the tissues removed.

Since a conclusive opinion regarding the value of thymectomy in myasthenia gravis cannot be given at this time, we propose to study with similar care the results in a larger series of cases, perhaps 100, over a longer period. We shall then compare the course of myasthenia gravis in the group subjected to surgical removal of the thymus gland with the course in a control group of patients who have not had the thymus gland removed. Much more time will be required for such a study, but only in this way can the possibility of false conclusions be avoided.

Analysis of Results.—The clinical data pertaining to the first 32 cases of myasthenia gravis in which the thymus gland was removed are presented in tables 1 and 2. The cases are grouped according to whether or not operation had been followed by improvement for the period ending June 1, 1946, at which time the data concerned with that part of the study were assembled. As has been pointed out, improvement was not necessarily attributed to the operation. The results are summarized in table 3.

First, it may be noted (table 3) that there were 15 cases of thymoma in this series of 32 cases. The large number of cases of thymoma is accounted for by the fact that early in this study only patients with roentgenologic evidence of a tumor in the anterior part of the mediastinum were advised to undergo surgical treatment. Later in the course of the study, thymectomy was offered the myasthenic patient as a possible means of influencing favorably the fundamental course of the disease. Similar advice is given such patients at present. Consequently, the proportion of cases of thymoma has decreased precipitously.

In 1 case of thymoma the patient died on the third day after operation, when she suddenly stopped breathing after the exertion entailed by the administration of an enema. In only 3 cases were patients with thymomas unimproved at the time the evaluation was made. One patient was less well than before operation; the other 2

TABLE 3.—*Results of Removal of Thymus Gland: 15 Myasthenic Patients with Thymic Tumor and 17 Patients Without Such Tumor*

Group 1:	Patients subjected to operation for removal of thymoma		15
	Died since operation (third day)	1	
	Not improved	3	
	Moderately improved	4	
	Considerably improved	7	
Group 2:	Patients subjected to operation for removal of thymus gland (no tumor)		17
	Died since operation (3 days; 3 months; 6 months)	3	
	Not improved	6	
	Moderately improved	5	
	Considerably improved	3	

were somewhat better subjectively. In 4 cases of thymoma the condition was moderately improved. This classification of results is limited to those patients who, at the time this study was completed, were not only better subjectively but could substantiate their claim of improvement by demonstrating that they could be as active as formerly on a significantly reduced intake of neostigmine or that they could do substantially more work on the same amount of neostigmine. Case 5 (table 1) is an example of moderate improvement. Before roentgen irradiation and removal of the thymoma, the patient had been unable to work as a farmer while taking 60 mg. of neostigmine bromide a day. His improvement after operation was gradual, and three and a half years later he was working as a farmer but was "unable to do a full day's work." He used neostigmine only occasionally, in doses of 15 to 30 mg. of the bromide per day.

Seven patients in this series of 15 with thymomas were classified as showing considerable improvement. In this category are grouped those patients who, at the time this study was completed, had entirely

recovered or who were able to live normally and could maintain themselves on a greatly reduced amount of neostigmine. Case 10 (table 1) is an example of what is meant by considerable improvement. The patient showed severe generalized muscular weakness while he was taking 75 mg. of neostigmine daily. Improvement appeared subjectively after operation, and by the sixth month it was obvious. Two years and four months later he was working full time as an educator, required only ephedrine and could indulge in physical work, whereas previously his arms had been so weak that he could not raise them over his head. Case 13 (table 1), our first case in which surgical operation was employed, is an example of complete remission after roentgen irradiation and surgical removal of a thymoma. Although the patient had been unable to work as a farmer with a dose of 135 mg. of neostigmine bromide daily, four and a half years later, at the age of 59, he was able to work hard as a farmer every day, had no symptoms of myasthenia gravis and was taking no medicine.

The thymomas in cases 4, 6 and 7 (table 1) were inoperable because they either had invaded such neighboring structures as the innominate vein and lung or had implanted themselves widely on the pleural surfaces. Of course, the moderate improvement occurring in case 4 cannot be attributed to surgical intervention. If the improvement is of significance, credit must be given to the intensive roentgen therapy administered after operation. In cases 1, 12 and 15, small amounts of thymic tissue attached to surrounding structures were left in place, but the bulk of the tumor tissue was removed successfully. In these cases roentgen irradiation was used after operation.

It is of interest to note the age and sex of the patients who had thymomas. Eleven were men and 4 women. The ages ranged from 26 to 57 at the time of operation, the mean being 45 years. Since there were approximately as many men as women in the total series, the preponderance of men in the group of 15 patients with thymomas would seem to indicate a tendency for the thymomas to occur in men. However, when the age at onset of the disease and the sex of the patients are charted (fig. 1) for a group of 100, it is seen that men predominated approximately in the ratio of 2:1 in the group in which the onset of myasthenia gravis occurred after the age of 40 years. Consequently, the larger number of men in the group with thymomas does not necessarily, in itself, reflect a tendency for thymomas to develop in men, but simply indicates that thymomas are found more frequently in older patients, who, in turn, are more likely to be men.

It is of some importance to learn that in 2 cases (1 and 3) roentgenologic evidence of the thymoma had been found before onset of the symptoms of myasthenia gravis. In 2 other cases (4 and 9) thoracic pain, which preceded the onset of symptoms of myasthenia

gravis, was of such character as to lead us to presume that the tumor had appeared before the myasthenia gravis. In case 5 (table 1) it is reasonable to suspect that the highly calcified and degenerated tumor found at operation seventeen months after the onset of symptoms must have been present long before the appearance of myasthenia gravis.

In the group of 17 cases in which thymomas were not present but the patient underwent operation, the results appear not to have been so good, since in only 8 was there unequivocal improvement at the time the data were assembled (table 3). This discrepancy may be more apparent than real if one takes into account that 4 of the 6 patients classified as unimproved had been followed from only six to seven and a half months. From a study of the records of cases in which improve-

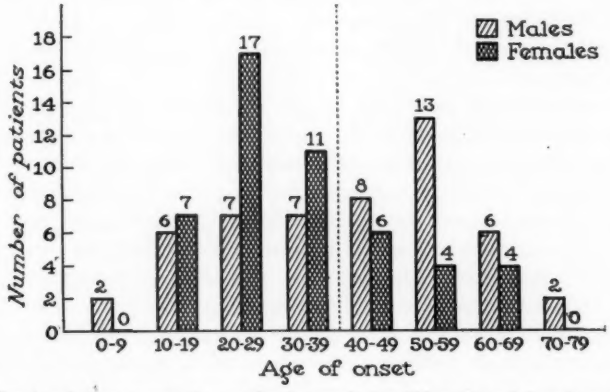

Fig. 1.—Age at onset of myasthenia gravis for 100 male and female patients.

ment occurred, we learn that even when decided improvement has taken place it seldom has been of significant degree within nine to twelve months after operation.

In 1 of this group of 17 cases in which thymomas did not exist, the patient died during immediate postoperative convalescence. He was a man, aged 67, who would not have undergone surgical treatment had there not been a mistaken roentgenologic diagnosis of "thymic tumor." However, as pointed out earlier in this communication, this case represents the only error in the roentgenologic diagnosis of thymic tumor thus far detected in our series. In this particular case an insignificant amount of thymic tissue was discovered. The same thing was true in case 19, and consequently the failure of the patient to improve is understandable.

So far as we can ascertain, no patients except those who died a few days after operation were made worse by operation. The 2 patients

who died three and six months, respectively, after operation were not helped, and their symptoms, which had been steadily progressing in severity, continued to progress.

An analysis of these records fails to show any significant correlation between the duration of symptoms of myasthenia gravis at the time of operation and the result obtained by removal of the thymus gland. For instance, in the group who underwent thymectomy but did not have thymoma, the average duration of the disease at the time of operation was three to four years, in both the 8 patients who showed definite improvement and the 8 patients who failed to receive benefit. That a long duration of the illness is not a contraindication to thymectomy is demonstrated by the good results obtained in cases 15 and 31, in which the onsets dated back to nine and six years before operation. Furthermore, there seems to be no significant correlation between the response to thymectomy and the length of time that neostigmine had been used in treatment.

We are unable to make any definite correlation between the result of operation and the pathologic observations except that as a whole the group who had thymoma did better than the group who did not have thymoma. Histologic evidence of thymic hyperplasia was present in 4 of 8 cases in which improvement did not follow thymectomy (no tumor), whereas in only 4 of the 8 cases with improvement was there evidence of hyperplasia. This aspect of the problem will be discussed in more detail in the section on "Pathologic Aspects."

In cases 1, 3 and 15, it is of interest to note that the patients laid considerable emphasis on loss of their sense of taste for periods up to several months during the course of illness. This was an important complaint in 3 other cases not included in this series, in 2 of which there was unequivocal roentgenologic evidence of thymoma. The significance, if any, of this complaint in myasthenia gravis is unknown to us.

SURGICAL ASPECTS

One of us (Clagett) has been the surgeon chiefly interested in thymectomy at this clinic, operating on all the patients in this report except those in cases 5 and 15, in which Dr. S. W. Harrington was the surgeon. The surgical aspects have been covered by us (Clagett, Eaton and Glover [14]) in other communications; in this report, we shall simply summarize this experience.

Selection of Patients for Surgical Treatment.—Eleven myasthenic patients presenting definite roentgenologic evidence of thymic tumor were advised to undergo operation unless two contraindications were

14. Clagett, O. T.; Eaton, L. M., and Glover, R. P.: Thymectomy for Myasthenia Gravis: Surgical Technic, Surgery, to be published.

present: (1) definite clinical and roentgenologic evidence that the tumor had implanted itself widely within the thoracic cage (1 case); and (2) clinical evidence that the condition of the patient was such as to make the risk of surgical exploration unreasonably excessive. Patients without roentgenologic evidence of tumor were not urged to undergo thymectomy. The experimental nature of the procedure was explained carefully and the patient was offered thymectomy as a procedure which might possibly influence the fundamental course of his or her disease favorably. Of course, persons who have the milder degrees of myasthenia gravis, particularly if the course is not progressive, are seldom interested in surgical treatment.

Preoperative Treatment.—The patient was usually placed in the hospital for two or three days before operation, where he would not be exposed to infections of the respiratory tract. Penicillin was administered for a day or two preceding operation. The patient was kept at rest, and the optimal dose of neostigmine and ephedrine was administered. Natural fluctuations in the severity of the disease were taken into acount, and surgical procedures were performed when the patient was at his best. For instance, since in women the symptoms of myasthenia gravis tend to be more intense during the week or two preceding the onset of the menses,[15] operation is postponed until this period has passed. It is carried out during the first two weeks of the menstrual cycle, when the patient is at her best. If a patient's condition is such as to make the risk of operation excessive, we have resorted to roentgen irradiation of the thymic area, in an effort to secure a remission, at which time, if remission is obtained, operation may be undertaken with less risk.

Operation.—A variety of surgical approaches to the thymic tumor were used.[14] Occasionally, the tumor was approached posterolaterally, after resection of a rib. At other times, when the tumor presented itself at one side or the other of the sternum, the tumor was removed after resection of the costal cartilages on that side. Although these two approaches often are advantageous from the standpoint of removal of the tumor, they do not allow for removal of other thymic tissue which may be present. At present, we agree with Blalock that the preferred surgical approach is obtained by splitting the sternum. In cases 2, 3, 5, 6, 9, 10, 13 and 15 the sternum-splitting approach was not used; consequently, we are not certain that all thymic tissue was removed.

During the operation, which usually requires thirty to fifty minutes, neostigmine methylsulfate may be administered parenterally. As a rule, however, the preoperative dose of 0.5 to 1.5 mg. of neostigmine methylsulfate is sufficient.

15. Ciaramelli, L. C., and Eaton, L. M.: Unpublished data.

The anesthetic agent preferred is a combination of nitrous oxide, oxygen and ether. An intratracheal tube is inserted routinely for administration of the agent.

Postoperative Treatment.—After operation, the patient is placed in an oxygen tent. He receives neostigmine methylsulfate parenterally every two to three hours or oftener, as required. From 0.5 to 1.5 mg. is usually used in each dose, depending on the patient's response. Ephedrine and atropine frequently are administered concomitantly.

It is of utmost importance that a clear airway be maintained. If needed, a mechanical aspirator should be at hand for removal of secretions from the pharynx. Splendid cooperation from anesthetists and bronchoscopists has been obtained; the results of maintenance of a clear airway by means of bronchoscopic aspiration have been important, since attention to this detail has enabled several of our patients to survive the immediate postoperative course.

As a rule, use of the oxygen tent and the parenteral administration of neostigmine can be discontinued on the second or third day after operation. The patient then receives orally whatever medication is required.

The importance of a Drinker type of respirator cannot be overemphasized. Its use has been of exceptional importance in several cases. If oxygenation is inadequate, the patient becomes apprehensive and exhausts himself. The improvement in the condition of several patients has been phenomenal after rest was secured by placing of the patient in the respirator, removal of inspissated material from the trachea and bronchi by means of the bronchoscope and administration of morphine sulfate, a drug which otherwise must be used sparingly with these patients.

In the average case the patient is allowed to be out of bed on the fourth or fifth day and to leave the hospital seven to ten days after operation. Only 2 patients of this series required hospital care longer than two weeks. Roentgen irradiation of the thymic area was used after operation in those cases in which there was not reasonable assurance that all thymic tissue had been removed. On dismissal from the hospital, the patient is instructed to resume normal activities and to reduce his medication as rapidly as his condition warrants.

PATHOLOGIC ASPECTS

Up to the present, we have been unable to demonstrate that any curare-like substance is present in extracts of thymomas. In 3 cases (3, 9 and 14), both isotonic saline extracts and alcohol extracts were prepared by Dr. H. L. Mason. Dr. J. L. Bollman injected these extracts

into mice and failed to detect any myasthenic-like effect. It is possible that future investigations with more sensitive technics will lead to positive results.

The most pertinent pathologic data regarding the thymic tumors are presented in table 4. The thymomas varied from a size of 2.5 by 3.5 by 2 cm. and a weight of 12 Gm. (case 11) to a size of 15 by 12 by 6 cm. and a weight of 462 Gm. (case 15). Four of the tumors

TABLE 4.—*Pathologic Data in Group 1: 15 Cases of Thymoma with Thymectomy*

Case No.	Weight of Thymoma, Gm.	Measurement of Thymoma, Cm.	Invasion of Surrounding Structures	Cyst Formation	Calcium Deposits	Necrosis	Roentgen Irradiation (Time Given Before Operation)	Per Cent Epithelium-like Cells	Per Cent Thymocytes
Patient Died Since Operation									
1.....	102	7 × 5 × 5	+	—	—	—	—	80	20
No Improvement									
2.....	96	7.5 × 6 × 6	—	—	+	—	—	60	40
3.....	..	7 × 4 × 3	—	+	+	+	5+ and 3 mo.	50	50
4.....	..	Biopsy	+	—	—	—	6 and 3 mo.	50	50
Moderate Improvement									
5.....	..	Removed piecemeal	—	+	+	+	5 mo.	5	95
6.....	..	Biopsy	+	—	—	—	6½, 6 and 5 mo.	90	10
7.....	..	Biopsy	+	—	—	—	—	75	25
8.....	28	7 × 4 × 2	—	—	—	—	1+ yr.	40	60
Considerable Improvement									
9.....	..	5 × 5 × 5	—	—	+	+	3— yr. to 7 mo. (4 courses)	5	95
10.....	30	7 × 4.5 × 3	—	+	—	—	—	5	95
11.....	12	2.5 × 3.5 × 2	—	—	—	—	—	50	50
12.....	12	4 × 2.5 × 2.5	+	—	+	+	7 mo.	10	90
13.....	70	6 × 5 × 4	—	—	—	—	4 mo.	40	60
14.....	26	6 × 4 × 3	—	—	—	—	—	60	40
15.....	462	15 × 12 × 6	+	+	+	—	—	5	95

were cystic, and 6 contained calcium, of varying amounts. Six were observed, at operation, to have invaded surrounding structures, and 3 were inoperable, only specimens for biopsy having been removed. Histologic examination failed to show any essential differences between the lesions which were invasive and those which were not. Four of the tumors showed necrosis, of varying degrees. In case 9, the central seven eighths of the tumor was necrotic (fig. 2). The necrosis may well have resulted from rather intensive roentgen irradiation, administered in four courses, the first almost three years and the last seven months before operation.

One of us (McDonald) has studied these tumors and thymus glands intensively and, with Dr. Murray, has published a report of them.[16] The tumors were composed of two types of cells. One type, the thymocyte, is identical with the small lymphocyte seen in lymph nodes. The other type is oval, about three or four times as large as a lymphocyte and contains a faint acidophilic cytoplasm. The nucleus of this oval cell stains lightly with hematoxylin. The cell is morphologically indistinguishable from the very young cells which line minute capillaries. The origin of this cell is questionable, and in the present report it is designated as the "epithelium-like cell." The proportion of thymocytes and epithelium-like cells varied widely from case to case. In 4 cases the thymocytes were estimated to compose as much as 95 per cent of the tumor, whereas in another case the epithelium-like cell was predominant to the same degree. In the rest of the tumors varying proportions of the two cell types, between these extremes, occurred.

Fig. 2 (case 9).—Cut surface of two halves of the thymoma. The central seven eighths of the tumor was necrotic.

In spite of careful study of the subject, we have found it extremely difficult to state with certainty whether or not a given thymus gland removed at operation is hyperplastic (table 5). Obviously, the weight of tissue removed at operation is not an adequate criterion, since the amount of fat and fibrous tissue in the specimen varies greatly. At present, the determination of hyperplasia depends on the following factors: (1) the amount of tissue present, (2) the proportions of thymic and fat tissues in the mass and (3) the age of the patient. The last point is important, since it is known that the adipose connective

16. Murray, N. A., and McDonald, J. R.: Tumors of the Thymus in Myasthenia Gravis, Am. J. Clin. Path. **15**:87-94 (March) 1945.

tissue is found to increase and the thymic tissue to decrease in progressive age groups. Hammar's [17] statistics on this subject are probably the most reliable. A thymus gland which may be considered normal in a patient 20 years old would be considered hyperplastic in a patient 50 years old. In any event, the problem of determination of whether or not a thymus gland is hyperplastic is not a static one; consequently, the designations used in the tables of this study with respect to hyperplasia and absence of hyperplasia must be considered tentative.

TABLE 5.—*Pathologic Data in Group 2: 17 Cases of Thymectomy But No Thymoma*

Case	Age, Yr.	Tissue Removed at Operation, Gm.	Percentage Thymic Tissue	Percentage Fat Tissue	Hyperplastic Thymus	Roentgen Treatment (Time Given Before Operation)
		Patient Died Since Operation				
16	67	22	1	99	—	—
17	26	24	90	10	+	—
18	40	19	50	50	+	—
		No Improvement				
19	52	Very little	5	95	—	—
20	30	14	60	40	+	—
21	24	23	80	20	+	3+ yr.
22	22	11	40	60	—	—
23	16	16	80	20	+?	2+ yr.
24	24	24	80	20	+	2 yr.
		Moderate Improvement				
25	52	..	10	90	—	6+ mo.
26	30	8	80	20	+?	—
27	22	36	75	25	+	—
28	43	42	15	85	+?	—
29	18	28	60	40	—	—
		Considerable Improvement				
30	17	25	80	20	+	—
31	23	12	20	80	—	5— mo.
32	27	8	60	40	+?	—

REPORT OF TEN CASES

In this section, we shall report 10 of the complete series of 32 cases. We shall describe 5 cases in which there was a tumor of the thymus gland and 5 cases in which there was no such tumor. The numbers given to the cases in this report will correspond to the numbers given to cases elsewhere in this paper and in tables 1, 2, 4 and 5. Since 22 cases have been omitted from this report, numbers given to cases in this particular section are not consecutive.

17. Hammar, J. A.: Die Menschenthymus in Gesundheit und Krankheit, Leipzig, Akademische Verlagsgesellschaft M. B. H., 1926, vol. 1.

Cases in Which There Was a Tumor of the Thymus Gland.—CASE 1.—*History.*—A Negro woman aged 40 was admitted to the clinic on March 18, 1943. In 1938 she had lost her sense of taste for sweets, and soon for all other things, for three months. In January 1941 she had had symptoms of an infectious disease which had been diagnosed as "flu." She had been confined to bed for ten days. Three weeks after recovery she had become ill with "pneumonia" and was confined to bed for three weeks. At this time roentgenograms of the thorax had been made, and the patient had been told that she had an abscess at the root of the lung.

In August 1941 the first definite symptom of myasthenia gravis had appeared, that is, ptosis of the right eyelid. A day or two later she had experienced a severe attack of "migraine." With this, she became nauseated and vomited, and her bowels did not move. She was confined to a hospital for five weeks, during which time she noticed occasional diplopia. By Oct. 15, 1941 she was able to resume her occupation of teaching. Ptosis of the right eyelid and diplopia continued to

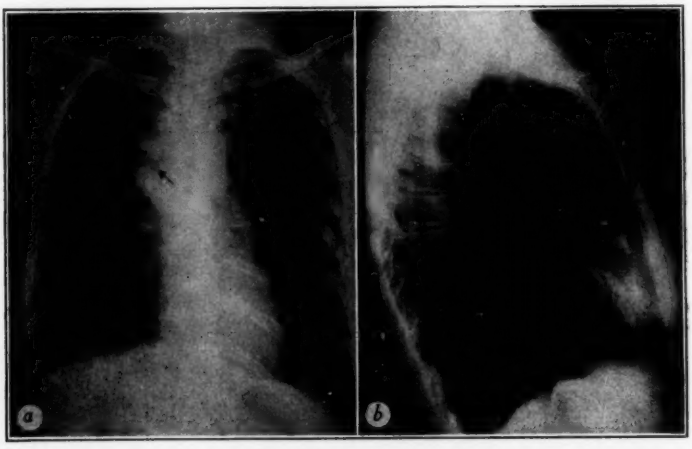

Fig. 3 (case 1).—(*a*) Thymoma projecting to the right of the sternum; (*b*) lateral view of the same lesion, showing the thymoma in the anterior part of the mediastinum.

occur from time to time. In January 1942 ptosis of the left eyelid became evident. In July 1942 an operation for correction of ptosis was performed on both eyelids. By October 1942 she noticed weakness of the jaws on chewing. In January 1943 there were difficulty in swallowing, regurgitation of fluids through the nose, a nasal type of speech, occasional urinary incontinence and a sensation of pressure under the sternum. The patient stated that neostigmine had been administered parenterally, without improvement.

Clinical Examination.—Examination at the clinic showed the typical myasthenic facies and a considerable degree of muscular weakness everywhere, but severest in the muscles of mastication. The masseter and temporal muscles were conspicuously atrophic. Neostigmine methylsulfate (1.5 mg.) was administered subcutaneously, and examination twenty minutes later revealed moderate improvement in the strength of the tongue, facial muscles and extremities, but no detectable improvement in ptosis, rotation of the eyeballs or strength of the muscles of masti-

cation. Since ptosis, diplopia and inability to close the jaws were her chief complaints and these symptoms were not improved, the lack of subjective improvement was in striking contrast to the objective improvement in other muscles, the weakness of which was not her chief concern.

Roentgenologic Examination.—A well defined, oval tumor, about 6 cm. in diameter, projected to the right of the midline in the anterior portion of the mediastinum at the level of the arch of the aorta (fig. 3 *a* and *b*).

Operation.—On April 2, 1943 a sternum-splitting incision was made. A large tumor, lying immediately behind the sternum, extended into the right side of the

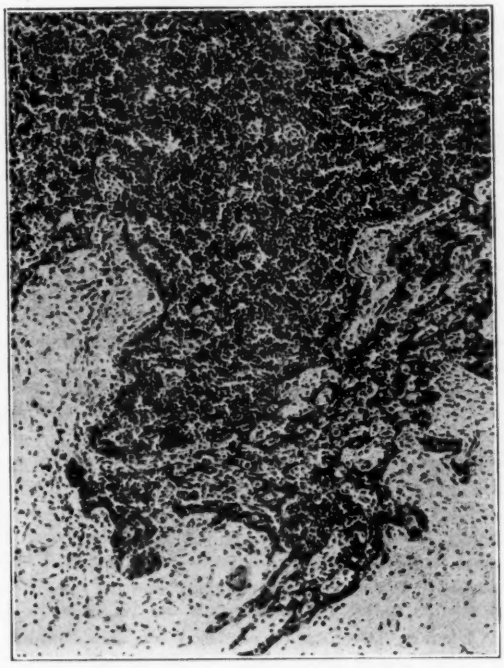

Fig. 4 (case 1).—Direct extension of tissue of the thymoma into the wall of the vena cava; hematoxylin and eosin stain, × 100.

thorax. It was adherent to the pericardium. On the right side it had invaded the pleura and the lung. A small portion of the upper lobe of the right lung was resected. The tumor was observed to be invading the superior vena cava (fig. 4); a small portion of the tumor was left on the vena cava as the lesion was dissected away. The innominate vein on the left was ligated and removed because of invasion of the vein by the tumor.

Pathologic Examination.—Grossly, the tumor presented a thick, fibrous capsule with fibrous trabeculae coursing through the tumor. The tumor was lobulated. It measured 7.5 by 6.0 by 6.0 cm. and weighed 96 Gm.

Histopathologically, the neoplasm was composed of pale spindle cells, often called epithelial, and thymocytes, in the approximate proportions of 60 and 40 per cent, respectively. The cells were attempting to form Hassall corpuscles and rosettes. Mitosis was not noted. There was minimal vascularity.

Postoperative Course.—The course was satisfactory until the third day, when, while the patient was using the bedpan, she suddenly stopped breathing, became cyanotic, failed to respond to neostigmine methylsulfate administered parenterally and died.

Necropsy.—Necropsy revealed nothing remarkable.

Case 3.—*History.*—A man aged 40, who was admitted to the clinic on Nov. 2, 1941, first noticed pain in the thorax in 1939 or 1940. Roentgenograms were made elsewhere, and the patient informed us that the diagnosis was dilated pulmonary conus. About November 1940 he lost his sense of taste for a few weeks. In June 1941 he began to complain that his ear felt as though it were stopped up. This sensation occurred intermittently. At about the same time he had occasional urinary incontinence. A month later, his lips became weak, his jaws began to tire on chewing, his speech became dysarthric, fluids regurgitated through the nose and he had some difficulty in swallowing. By October 1941 the upper extremities had become weak.

Clinical Examination.—The facial muscles were moderately weak; speech became unintelligible after two or three minutes of reading; the muscles of the shoulder girdle were extremely weak, and the more distally placed muscles of the upper extremities were moderately weak. The tone of the rectal sphincter was considerably reduced. The reaction to the neostigmine test was positive for myasthenia gravis. Urologic study revealed slight obstruction at the vesical neck. Cystometrograms made before and after the administration of neostigmine were not remarkable.

Roentgenologic Examination.—There was a flattened, oval tumor in the mediastinum, situated anterior to the hilus of the left lung. In the posteroanterior roentgenogram it appeared to be a part of the cardiac shadow. When first seen, it was called a "dilated conus." On roentgenoscopic inspection, the shadow appeared to pulsate as though it were a portion of the heart, and the roentgenoscopist confirmed the original diagnosis of "dilated conus." It was not until a second examination was made, after a course of roentgen therapy and a lateral roentgenogram of the thorax, that the true nature of the tumor was recognized (fig. 5 *a* and *b*).

Preoperative Course.—The patient's condition was much improved while he was taking 150 to 210 mg. of neostigmine bromide, 72 mg. of ephedrine sulfate and 1.0 Gm. of guanidine hydrochloride daily. On November 13 and 15, the thymic area was given roentgen irradiation through two anterior fields. The technical factors were: 130 kilovolts, 6 milliamperes, 6 mm. of aluminum filtration, 40 cm. distance and three minutes' exposure. The patient returned to work as superintendent in a factory.

He returned for reexamination on Feb. 3, 1942, stating that during the two previous weeks he had felt stronger and had reduced the intake of neostigmine slightly. Roentgenograms of the thorax showed no change. The second course of roentgen irradiation was administered on Feb. 3 and 4, 1942.

On May 4, 1942 the patient returned to the clinic. His condition was definitely improved, and he had reduced the dose of neostigmine bromide to 60 mg. daily. Roentgenograms of the thorax revealed an enlargement of the shadow previously interpreted as representing a dilated pulmonary conus.

Operation.—On May 7, 1942, a horseshoe-shaped incision was made on the left and anterior part of the chest. The cartilages of the second and third ribs were removed anteriorly. The internal mammary artery was ligated. A large tumor was observed bulging out into the left part of the thorax. It was densely adherent to the pleura. The portion of the tumor extending to the left was solid; the portion extending to the right was cystic. The cystic portion of the tumor was adherent to the pericardium. The tumor was removed completely.

Pathologic Examination.—The neoplasm measured 7 by 4 by 3 cm. It had a fibrous and calcareous capsule and was cystic. Little of the tumor contained neoplastic tissue, the main part being necrotic.

The tumor was composed of approximately the same number of thymocytes and epithelium-like cells. The tumor was highly vascular. Rosetting was ill defined. A few mitoses were present in the epithelium-like cells.

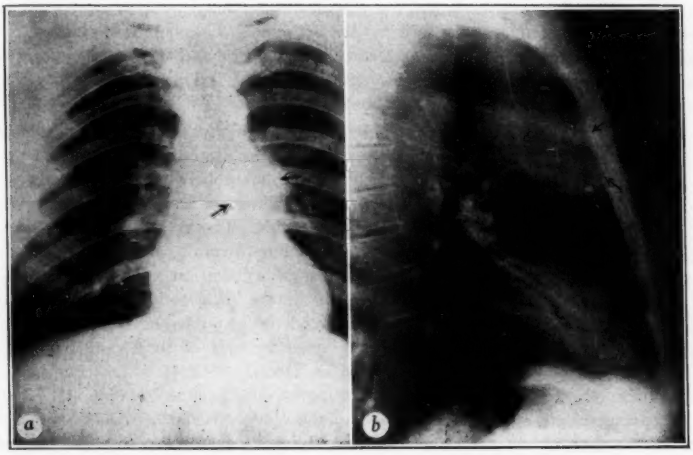

Fig. 5. (case 3).—(*a*) Thymoma situated at the left of the sternum, a lesion first erroneously diagnosed as "dilated conus"; (*b*) lateral view of the same lesion.

Postoperative Course.—The convalescence was uneventful except for the development of considerable restlessness, apprehension and confusion on the fourth day after operation. This reaction subsided gradually in the course of a few days, and the patient was allowed to leave the hospital eleven days after operation .

On March 27, 1944 he returned, stating that he was working full time and required 105 mg. of neostigmine bromide and 0.875 Gm. of guanidine hydrochloride daily. Difficulty in speaking was his chief complaint. He had received the third, fourth and fifth courses of roentgen irradition of the thymic region elsewhere.

The patient was last examined at the clinic in September 1945. His condition remained essentially stationary. At the time of this report, he was employed full time and continued to take 120 mg. of neostigmine bromide and 1.0 Gm. of guanidine hydrochloride daily. The sixth, seventh and eighth courses of roentgen therapy were administered in March 1944, March 1945 and September 1945, respectively, at his request.

Evaluation of Result.—There was no significant improvement. The course was not progressive at the time this study was completed.

CASE 6.—*History.*—A man aged 41 was admitted to a hospital on Sept. 30, 1942. An accurate history could not be obtained from the patient because of his mental dulness. Apparently, the first pertinent symptoms occurred in the winter of 1940 and 1941, when the patient complained of thoracic pain on breathing deeply. This pain was severe for a few days and thereafter was persistent, but less intense. About July 1941 ptosis of the right eyelid, diplopia, severe weakness of the arms and considerable difficulty in talking and swallowing developed. He lost 33 pounds (15 Kg.) in the succeeding two or three months. He had had scarcely any food or water during the preceding eight days.

Clinical Examination.—The patient arrived at a hospital in a serious condition, emaciated and dehydrated. Examination of the thorax revealed signs of pleural effusion on the left side. Although the tentative diagnosis of carcinoma of the lung with cerebral metastasis had been made by the internist who first examined him, it was decided to test the effects of neostigmine. One-half milligram of neostigmine methylsulfate was administered subcutaneously, and within fifteen minutes the patient surprised his physician by sitting up in bed, asking with a strong voice for water and drinking 2 glasses without difficulty.

Preoperative Course.—As soon as the diagnosis of myasthenia gravis had been established by the patient's dramatic response to neostigmine, the administration of 240 mg. of neostigmine bromide and 72 mg. of ephedrine sulfate daily was begun. From Oct. 5 to 12, 1942 roentgen irradiation of the thorax was carried out through two anterior and two posterior fields. The technical factors were: 130 kilovolts, 6 milliamperes, 6 mm. of aluminum filtration, 40 cm. distance and ten minutes' exposure. By Oct. 31, 1942 the patient's condition was much improved; he ate well and had gained weight, and the intake of neostigmine bromide had been reduced to 120 mg. daily. The second and third courses of roentgen irradiation, identical with the first course, were given from Oct. 28 to 31, and from Nov. 16 to 19, 1942. The patient was dismissed on Dec. 3, 1942, at which time he was ambulatory. He was then taking 90 to 120 mg. of neostigmine bromide and 72 mg. of ephedrine sulfate daily. He returned to the clinic on Feb. 27, 1943 because of pain in the thorax. At that time he was taking 90 mg. of neostigmine bromide daily, and his weakness was of slight degree two hours and forty-five minutes after he had taken 30 mg. of neostigmine bromide. He had not been working.

Roentgenologic Examination.—Pleural effusion was seen on the left, and the structures of the mediastinum were shifted to the right. An irregular mass could be seen, which projected into the left side of the thorax from its position in the anterior portion of the mediastinum.

Operation.—On March 16, 1943 a posterolateral incision was made on the left side. A segment of the fifth rib was resected, and the pleura was opened. Surgical exploration of the pleural cavity revealed 1 quart (0.95 liter) of fluid. Multiple tumor implants were seen on the pleura and were invading the lung. Some of these were studied for biopsy.

Pathologic Examination.—The specimen of a pleural implant taken for biopsy was ovoid and grayish and measured 3.5 by 2.5 by 2.5 cm. The tumor was composed of epithelium-like cells and thymocytes, in the ratio of 9:1. The tumor was fairly vascular and contained thick, fibrous trabeculae. Rosetting and Hassall corpuscles were not observed.

Postoperative Course.—The immediate postoperative course was uneventful. On March 25 another course of roentgen therapy was begun. Treatments were administered daily for eight days, two anterior and two posterior fields being irradiated twice. The technical factors were: 130 kilovolts, 6 milliamperes, 6 mm. of aluminum filtration, 40 cm. distance and twenty minutes' exposure. The treatments were completed on April 2, 1943, and the patient was dismissed, his condition being essentially the same as on admission.

We have had no word directly from this patient since his dismissal. Numerous letters of inquiry have been unanswered. However, we received word from a reliable source on Oct. 19, 1945, three years after the original admission of the patient, and two years and seven months after his last roentgen treatment, that the patient was irregularly employed at manual labor.

Evaluation of Result.—Obviously, no benefit can be attributed to the surgical exploration in this case, since the thymic tumor was found to be inoperable because of intrathoracic metastasis. There can be no reasonable doubt that the administration of neostigmine saved this patient's life. Furthermore, we have concluded that roentgen irradiation of the malignant thymoma deserves a degree of credit difficult to evaluate. Experience in similar cases, yet to be reported, strengthens our opinion that except for roentgen therapy, this patient would not have been alive three years later. We believe it is reasonable to include this patient in the group of those whose condition showed moderate improvement after surgical treatment.

CASE 9.—*History.*—A woman aged 26 was admitted to the clinic on Aug. 6, 1942. She remembered that for one day, when she was 12 years old, she had experienced severe pain over the sternum which she believed was identical with that which will be described later. Furthermore, she was of the opinion that from the age of 13 to 16 years she had noticed a sense of fatigue in the facial muscles. Apparently, however, nothing unusual in her expression had been recognized by others.

In September 1939, she complained of "knifelike" pain in the thorax. Because of this symptom, roentgenograms were made, which revealed a tumor in the mediastinum. A course of roentgen therapy was administered, and the tumor was said to have decreased rapidly in size. The second course of roentgen therapy was administered in May 1940.

In August 1940 definite symptoms of myasthenia gravis developed. Her lips became weak and her speech nasal in quality. Soon she complained of dysphagia, nasal regurgitation of fluids, tiring of the jaws and profound weakness of all extremities. At the height of her illness, in November 1941, there were attacks of dyspnea and occasional urinary incontinence.

A third course of roentgen irradiation of the thymic area had been administered in August 1941. Treatment with neostigmine bromide was begun in November 1941, and for a time the patient required 285 mg. of this drug daily. Remission began in December 1941. A fourth course of roentgen therapy was administered in January 1942. For about a month she was less well; she then began to improve again and was able to resume light work as a clerk while she was taking 90 mg. of neostigmine bromide and 72 mg. of ephedrine sulfate daily. By June 1942 her health was failing again, and she was forced to stop work. She required 120 to 150 mg. of neostigmine bromide and 72 mg. of ephedrine sulfate daily to remain ambulatory.

Clinical Examination.—The patient was found to have severe weakness of the facial muscles and moderate generalized weakness, which responded to the administration of neostigmine in a manner characteristic of myasthenia gravis.

Roentgenologic Examination.—A flattened, lobulated tumor was situated in the anterior portion of the mediastinum and was closely associated with the aorta. It could be seen only in the lateral roentgenogram. The routine posteroanterior roentgenogram showed no recognizable abnormality, and the tumor was not seen by the roentgenoscopist (fig. 6*a* and *b*).

Operation.—On Aug. 17, 1942 a posterolateral incision was made on the right side. A long segment of the fifth rib on the right was removed. The pleura was opened. A firm, rounded tumor was encountered just behind the sternum at about the level of the second and third cartilages, anteriorly. Tissues were adherent to the tumor, probably as a result of roentgen therapy. The tumor was dissected from the superior vena cava and pericardium.

Pathologic Examination.—The tumor was approximately 5 cm. in diameter, and the central seven eighths was necrotic (fig. 2). A small amount of tumor

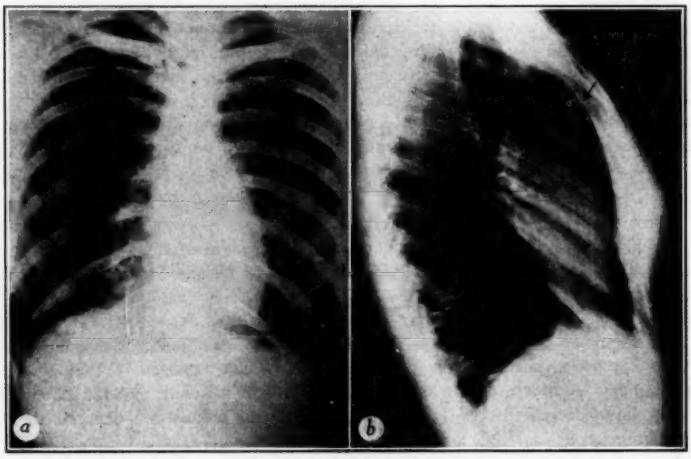

Fig. 6 (case 9).—(*a*) Posteroanterior roentgenogram of thorax, in which the thymoma was not seen; (*b*) thymoma visible in the lateral view, as indicated by arrow.

tissue was observed to contain approximately 95 per cent thymocytes and 5 per cent epithelium-like cells. There were well defined Hassall corpuscles, containing calcium. Vascularity was rather pronounced. No definite rosetting was observed. There were a few lymph follicles.

Postoperative Course.—Convalescence was essentially uneventful, and the patient was dismissed on the fourteenth day after operation. From Sept. 7 to 10, 1942, the thymic area was irradiated through two anterior and two posterior fields. The technical factors were: 130 kilovolts, 6 milliamperes, 5 mm. of aluminum filtration, 40 cm. distance and eight minutes' exposure. The output per field was 252 r.

At the time of the patient's dismissal from the clinic, on September 10, she was taking 120 mg. of neostigmine bromide and 72 mg. of ephedrine sulfate daily. By Nov. 12, 1942 she was teaching school and taking 90 mg. of neostigmine bromide and the usual dose of ephedrine sulfate daily. In January 1943 she wrote that she was not so well and that she had increased the dose of neostigmine bromide to

150 mg. daily. On March 19, 1944 she was feeling stronger in spite of a cold; at this time she required 90 mg. of neostigmine bromide. When she was last heard from, on Feb. 28, 1946, three and a half years after the operation, she was regularly employed and feeling greatly improved; she required 45 mg. of neostigmine bromide and 72 mg. of ephedrine sulfate daily and was very much pleased with the result, which she attributed to the operation.

Evaluation of Result.—The patient was considerably improved, and was still gradually improving, three and a half years after operation. The marked fluctuations in the course of the illness had disappeared. The remissions experienced before operation seem to have resulted from roentgen irradiation of the thymus gland.

CASE 10.—*History.*—A man aged 45 was admitted to the clinic on Dec. 13, 1943. On Nov. 4, 1943 the patient noticed that his arms were so weak that he had difficulty in hanging his coat on a hook. Later, while he was raking, his arms became weak, but strength returned after resting. On November 11 ptosis of the left eyelid developed. At this time the diagnosis of myasthenia gravis was made by an ophthalmologist, and the administration of neostigmine bromide was begun. The patient's condition became much improved by the taking of 75 mg. of the drug daily. His weakness continued to progress, however; and on December 1 dysphagia, dysarthria, nasal speech and weakness of the muscles of mastication developed.

Clinical Examination.—Tests of muscular function at 10:30 a. m., one and a half hours after the administration of 15 mg. of neostigmine bromide, revealed moderate weakness of the muscles of mastication, the neck, the triceps brachii and the iliopsoas muscles. The deltoid muscles were very weak. There were slight ptosis of the left eyelid and slight weakness of other muscles of the upper extremities.

Roentgenologic Examination.—A flat, poorly defined tumor was situated near the base of the heart in the anterior portion of the mediastinum. It seemed to form a part of the shadow of the heart and great vessels. The lesion was not seen on two occasions when stereoscopic posteroanterior roentgenograms were the only form of examination. It was first found during roentgenoscopy and was later identified on lateral roentgenograms.

Operation.—On December 17, a horseshoe-shaped incision was made on the right side over the third and fourth cartilages. The third and fourth cartilages were removed, and the anterior part of the mediastinum was explored extrapleurally. A well encapsulated thymic tumor was observed in the upper part of the pericardium. It was removed without difficulty. No other thymic tissue was seen.

Pathologic Examination.—The tumor measured 7 by 4.5 by 3 cm., weighed 30 Gm. and was partially cystic. It had a thick, fibrous capsule (fig. 7). The solid portion of the tumor comprised about half the entire mass and was whitish and very friable. The tumor was composed of approximately 95 per cent thymocytes and 5 per cent epithelium-like cells. Formation of Hassall corpuscles was seen, but there was only slight rosetting. There was no mitosis, and few fibrous trabeculae were present.

Postoperative Course.—Convalescence was relatively uneventful. The right deltoid muscle became almost completely paralyzed, and its strength was not significantly improved by the administration of 1 mg. of neostigmine methylsulfate. The patient was allowed to return home on Jan. 5, 1944, at which time he showed no improvement. He was reexamined on June 14, when there was no objective improvement. At that time he was taking 120 mg. of neostigmine bromide and

72 mg. of ephedrine sulfate daily. Roentgen irradiation to the thymic area through two anterior and two posterior fields was carried out from June 15 to 19. The technical factors were: 130 kilovolts, 6 milliamperes, 5 mm. of aluminum filtration, 40 cm. distance and seventeen minutes' exposure. The output per field was 544 r, measured in air. In August 1944 and in April 1945, he wrote that he was improving steadily, and examination in June 1945 verified his statements. At that time he required 15 mg. of neostigmine bromide and 72 mg. of ephedrine sulfate daily and was able to perform his duties as superintendent of schools. Roentgen irradiation of the thymic area was repeated with the same technic as that used in June 1944. When he was last heard from, on April 16, 1946, two years and four months after operation, he wrote: "My condition is improved. I take ⅓ grain [24 mg.] of ephedrine sulfate before each meal. Often I miss the one before the noon meal without too much reaction. The neostigmine is not needed much now. I often go

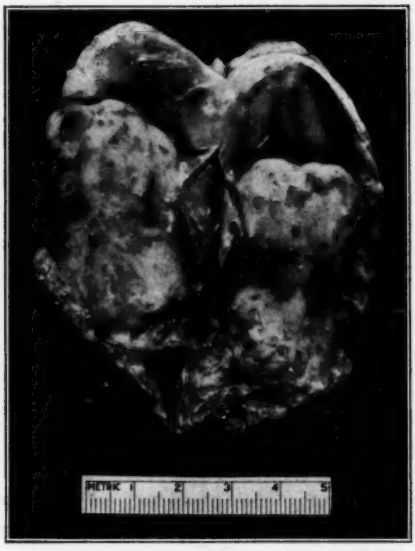

Fig. 7.—Thick, fibrous capsule and cystic portion of the thymoma removed in case 10.

several days without as much as ½ tablet [7.5 mg.]. Never do I take more than ½ tablet per day, and that is in midafternoon.

"My speech has improved so that I am able to speak about as well as ever. My muscular condition is very good."

Evaluation of Results.—The patient showed considerable improvement.

Cases in Which There Was No Thymic Tumor.—CASE 18.—*History.*—A woman aged 40 was admitted to the clinic on May 18, 1945. In February 1945, she had noticed that her arms tired excessively after work and on combing her hair. A few days later, she could not close her jaws tightly after chewing. She was given thyroid and became worse. Within two weeks of the onset of her difficulty she had nasal speech, regurgitation of fluids through the nose and diplopia. Forty-five milligrams of neostigmine bromide was administered daily, without much

improvement. On March 3, administration of the thyroid was discontinued, and the dose of neostigmine bromide was increased to 75 mg. daily, with considerable improvement. However, the patient's symptoms continued to become more intense. At the time of admission to the clinic she was unable to do any useful work, in spite of the taking of 300 mg. of neostigmine bromide and 100 mg. of ephedrine sulfate daily.

Clinical Examination.—Tests of muscular function revealed generalized muscular weakness, which was considerably improved after the administration of neostigmine bromide.

Roentgenologic Examination.—No evidence of thymic tumor was found.

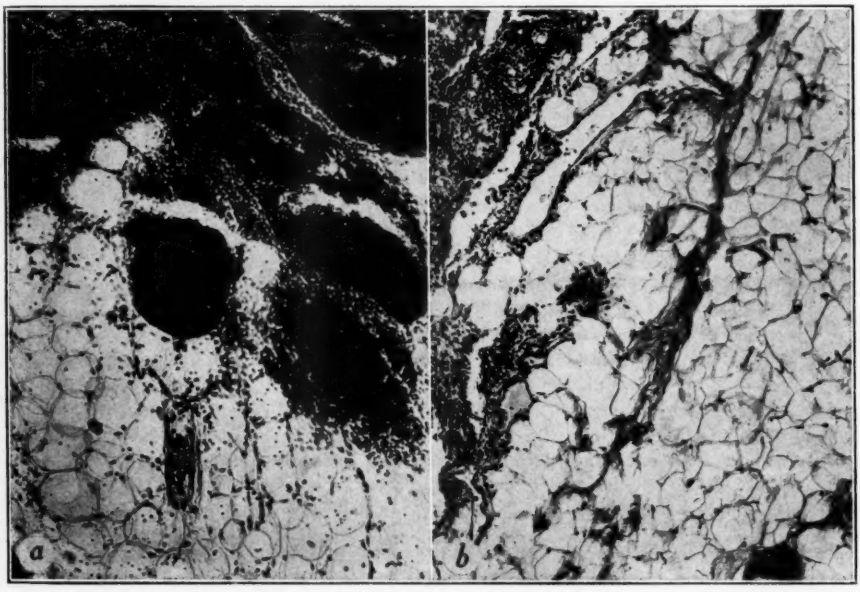

Fig. 8.—Hyperplasia of the thymus in a patient 40 years of age (case 18); hematoxylin and eosin stain, × about 90. (*b*) Nonhyperplastic thymus gland in case 25. The gland was composed of about 90 per cent fat and 10 per cent thymic tissue; hematoxylin and eosin stain, × about 90.

Operation.—On May 29, 1945, a sternum-splitting incision was carried out, and a large, hyperplastic thymus gland was encountered. The gland was of the typical bilobed variety. It was removed completely, without difficulty.

Pathologic Examination.—The tissue removed was an irregular mass of thymic tissue, measuring 5 by 4.5 by 0.3 cm. and weighing 19 Gm. The specimen was composed of 50 per cent thymus tissue and 50 per cent fat, with some fibrous tissue. There were well defined Hassall corpuscles and a few follicles. The thymus gland was hyperplastic (fig. 8*a*).

Postoperative Course.—Convalescence was relatively uneventful. She was allowed to leave the hospital and to return to her home on the fourteenth day after

operation. At home she failed to improve and remained bedfast. The dose of neostigmine was increased. Her physician reported that on Aug. 28, 1945, three months after operation, her respirations became slow, slight cyanosis developed and she lost consciousness and died within a few minutes.

Necropsy.—Necropsy was not performed.

CASE 22.—*History.*—A man aged 22 was admitted to the clinic on Jan. 5, 1944. In July 1942, while he was rowing a boat in a race, he had rather suddenly lost the strength in his upper and lower extremities. He seemed to recover in a half-hour and climbed up a rope ladder without difficulty. After that, his endurance gradually failed, and less and less exertion was required to bring on weakness of the extremities. He had noticed diplopia on occasion but had never been aware of ptosis or difficulty with the muscles supplied by the brain stem.

Clinical Examination.—Examination revealed nothing significant except for slight weakness of the deltoid muscles. After he had taken 20 grains (1.3 Gm.) of quinine sulfate, he was moderately weak in the extremities, but strength returned rapidly after the administration of neostigmine methylsulfate. Less than a tenth of the average clinical dose of solution of curare produced a decided weakening effect.

Roentgenologic Examination.—There was no evidence of thymic tumor.

Preoperative Course.—The patient required 90 to 120 mg. of neostigmine bromide and 72 mg. of ephedrine sulfate daily in order to work as a salesman.

Operation.—On Aug. 17, 1945 a sternum-splitting incision was made. A typical bilobed type of thymus gland was removed without difficulty.

Pathologic Examination.—The specimen measured 9 by 3.5 by 5 cm. and weighed 11 Gm. The specimen consisted of 40 per cent thymus tissue and 60 per cent fat and fibrous tissue. There were well defined Hassall corpuscles, but no follicles. The thymus gland was nonhyperplastic.

Postoperative Course.—The immediate convalescence was uneventful, and the patient was dismissed from the hospital seven days after the operation.

When he was last heard from, on April 4, 1946, almost eight months after operation, his condition was essentially the same as it had been during the preoperative period of observation.

Evaluation of Result.—There was no improvement eight months after thymectomy.

CASE 25.—*History.*—A woman aged 52 was admitted to the clinic on April 27, 1942. During the autumn of 1936 she had noticed diplopia and ptosis. In 1940 an operation was performed elsewhere on both eyelids to overcome the ptosis. In the spring of 1941 the patient became worse. Tiring of the muscles of the jaws, dysphagia, regurgitation of fluids through the nose and difficulty in talking developed. At that time her physician began treatment with 30 mg. of neostigmine bromide and one injection of 0.5 mg. of neostigmine methylsulfate daily.

Clinical Examination.—On examination the patient was found to have bilateral ptosis of severe degree; weakness of the extraocular muscles, particularly the right lateral rectus; severe weakness of the facial muscles, and moderate weakness of the muscles of the shoulder and pelvic girdles.

She required 150 mg. of neostigmine bromide daily for optimal results.

Roentgenologic Examination.—There was no evidence of thymic tumor.

Preoperative Course.—On May 5 and 6 the patient received roentgen therapy to the thymic area through two anterior fields. The technical factors were 130

kilovolts, 6 milliamperes, 5 mm. of aluminum filtration, 40 cm. distance and eight minutes' time per field.

She returned on June 23, 1942. Her condition was essentially unchanged. She continued to take 120 to 150 mg. of neostigmine bromide daily or 90 mg. of neostigmine bromide and 0.75 Gm. of guanidine hydrochloride. A second course of roentgen therapy, identical with the first, was administered.

The patient was reexamined on Dec. 2, 1942, at which time she showed definite improvement. She said she had begun to gain in strength soon after the second course of roentgen therapy, six or seven weeks after the first course. She was taking only 30 mg. of neostigmine bromide and 48 mg. of ephedrine sulfate daily.

Operation.—On Jan. 18, 1943, a sternum-splitting incision was made. A sheath of thymic tissue was found to extend from the manubrium to the upper portion of the pericardium. A bilobed type of gland was present. The entire thymus gland was removed.

Pathologic Examination.—The thymus gland was large and bilobed. The specimen was composed of 10 per cent thymus tissue and 90 per cent fat. There were a few Hassall corpuscles, but no follicles. The thymus gland was nonhyperplastic (fig. 8 *b*).

Postoperative Course.—The patient's postoperative course was exceptionally stormy. On the second day after operation she complained of difficulty in breathing, in spite of increasingly frequent doses of neostigmine methylsulfate. By 11:30 p. m. on the second day after operation she appeared to be moribund, gasping for breath and not responding to injections of 2.0 mg. of neostigmine methylsulfate. As an emergency measure, she was transferred to another hospital, where she could be placed in a respirator. In the respirator, she improved rapidly for a few hours, but by the fourth day after operation her condition again was critical. Roentgenograms showed the field of the right lung to be cloudy. Fluid could not be aspirated. Bronchoscopy was performed, and 50 cc. of thick, purulent material was aspirated from the trachea and the right main bronchus. After this procedure the patient improved rapidly, and the respirator was not needed after the seventh postoperative day. She was confined to the hospital until the twenty-second day after operation.

By March 19, two months after operation, her condition had improved to about that at the time of operation. On May 20 and 21, the third course of roentgen therapy was administered, largely because the patient desired it, since she attributed the improvement before operation to roentgen therapy. Furthermore, it was possible that some thymic tissue had been overlooked at the time of operation. The patient was next seen in June 1944, at which time she was able to do "quite a little" housework and was taking 60 mg. of neostigmine bromide and 72 mg. of ephedrine sulfate daily. The fourth course of roentgen therapy was administered. In September 1944, she returned, stating that she was delighted with her progress, was able to do eight hours of housework and was taking no medicine. Examination demonstrated that she was stronger, after not having had medication, than she had been while with it. The fifth course of roentgen therapy was administered. The patient returned for the sixth, and last, course of roentgen therapy in July 1945, stating that she had continued to improve. When she was last heard from, on April 5, 1946, three years and three months after operation, she continued to show moderate improvement and had taken neostigmine only occasionally. Although her general strength was much better, the ptosis and diplopia remained.

Evaluation of Result.—Moderate improvement persisted for more than three years after thymectomy and roentgen irradiation of the thymic area.

CASE 31.—*History.*—A man aged 23 was admitted to the clinic on Sept. 9, 1945. In 1938, while he was marching with a band in a parade, the patient found himself behind and discovered that he could not run to catch up. In the same year he had noticed weakness of his extremities while he was playing baseball. Since that time he had noticed unusual weakness of the upper extremities on such activities as carrying a suitcase for a long distance. By 1940 he noticed weakness of the legs in climbing stairs, and in 1941 he had difficulty in stepping up into a streetcar. In 1943 he became a navigator for an airline, and he had difficulty in climbing into the larger airplanes. In February 1944 the plane which he was flying nearly crashed in the ocean, through no fault of his; but, needless to say, this near-accident caused considerable emotional distress. Two days later he became weaker than ever. Ptosis developed bilaterally, and for the second time in his life the patient had difficulty in swallowing. His lips felt "stiff" after talking, and there was regurgitation of fluids through the nose. In March 1944, his physician administered an injection of neostigmine methylsulfate, which strengthened him greatly. Neostigmine bromide was prescribed. The patient found that his requirements of neostigmine varied greatly from day to day. Sometimes he was strong while he was taking only 45 mg. of neostigmine bromide daily; on other days he required as much as 225 mg.

In April 1944, ten roentgen treatments were administered to the thymic area. He received eight more treatments in May and June of the same year. His condition was not improved at the time of his admission to the clinic, in September 1945.

Clinical Examination.—Examination revealed bilateral ptosis of moderate degree and moderate weakness of the facial muscles and of the muscles of the upper and lower extremities.

Roentgenologic Examination.—There was no evidence of enlargement of the thymus gland.

Operation.—On Sept. 15, 1944 a sternum-splitting incision was made, and the anterior part of the mediastinum was exposed. A large, bilobed thymus gland, with lobes extending into the region of the thyroid gland, was completely removed.

Pathologic Examination.—The thymus gland was large and bilobed. It weighed 12 Gm. The specimen consisted of 80 per cent fat and 20 per cent thymus tissue. There were a few ill defined follicles and Hassall corpuscles. The thymus gland was nonhyperplastic.

Postoperative Course.—The patient's immediate convalescence was uneventful. He was dismissed from the hospital ten days after operation.

At reexamination, on April 16, 1945, seven months after operation, the patient was found to have increased strength. He had followed a sedentary occupation since Nov. 27, 1944. He took only 15 mg. of neostigmine bromide, or approximately 7 Gm. of potassium chloride, once in the afternoon.

On Sept. 19, 1945, one year after the operation, the patient wrote, "I am at least 90 per cent better than I was a year ago." For an average day of work at the office he required no medication. Once or twice a week he took 7.5 mg. of neostigmine bromide once during the afternoon.

When he was last heard from, in March 1946, one year and five months after operation, his condition had remained considerably improved. He was working full time and occasionally used 7.5 mg. of neostigmine bromide or approximately 7 Gm. of potassium chloride once a day.

Evaluation of Result.—Since this patient had myasthenia gravis for six years before removal of the thymus gland, and since the myasthenia gravis was becoming

progressively worse, so that he required 225 mg. of neostigmine bromide on some days, and since one year and five months after operation he was leading a normal life and seldom required minimal treatment, it is concluded that his condition was considerably improved.

CASE 32.—*History.*—A woman aged 27 was admitted to the clinic on June 19, 1944. In September 1941 she began to have ptosis of one or the other eye, but seldom of both at the same time. By October 1941 her speech had become nasal in quality. She became pregnant in February 1942 and gave birth to a daughter in November 1942. She experienced relatively little trouble from myasthenia gravis during pregnancy, but there was no perceptible abatement in her symptoms at this time. In June 1943, all four extremities became very weak, and she had difficulty in chewing and swallowing and began to lose weight. In September 1943, a diagnosis of myasthenia gravis was made, and treatment with neostigmine was started. She took 45 mg. of neostigmine bromide and 0.5 mg. of neostigmine methylsulfate daily.

Clinical Examination.—The facial muscles, soft palate and extraocular muscles were extremely weak. Ptosis and dysarthria were pronounced. The tongue and muscles of the neck and upper extremities were moderately weak. The condition of the patient was improved by an increase in the dose of neostigmine bromide to 90 mg. daily and by the addition of 48 mg. of ephedrine sulfate daily.

Roentgenologic Examination.—There was no evidence of thymic tumor.

Operation.—On Aug. 29, 1944 a sternum-splitting incision was made. A bilobed thymus gland was removed without difficulty.

Pathologic Examination.—The thymus gland was bilobed and weighed 8 Gm. It consisted of 60 per cent thymic tissue and 40 per cent fat. There were well marked Hassall corpuscles, with beginning calcification and a few follicles. The thymus gland was questionably hyperplastic.

Postoperative Course.—The convalescence of the patient was essentially uneventful. She was allowed to leave the hospital on the twelfth day after operation and to return to her home one day later. On Oct. 22, 1944 she reported by letter that she was much better except for her eyes, and that two weeks after leaving the hospital she had reduced the dose of neostigmine bromide to 30 mg. daily. By November 1944 she had discontinued the use of neostigmine altogether and was able to do light housework. By April 13, 1945, five months after operation, she was doing all the housework for a family of four and did not need medicine. When she was last heard from, on March 31, 1946, sixteen months after operation, she was doing heavy work in a veneer mill, without medication, and said, "I feel as strong as I did before I had myasthenia gravis."

Evaluation of Result.—The patient's condition was considerably improved.

SUMMARY AND CONCLUSIONS

Pathologists have accumulated convincing evidence that there is some relation of myasthenia gravis to the condition of the thymus gland.

Proper roentgenologic technic reveals evidence of thymic tumor in approximately 15 per cent of patients who have myasthenia gravis. Evidence has been presented to substantiate the claim that this figure closely approximates the true incidence of thymic tumor in this disease.

An analysis of the results obtained for 15 patients who had myasthenia gravis and associated thymic tumor and for 17 patients without thymic tumor who underwent operation for removal of the thymus gland shows that 60 per cent of patients were improved four and a half years to one-half year after operation. Although these results are encouraging, they must not be looked on as conclusive evidence that thymectomy is of value in the treatment of myasthenia gravis, since the course of myasthenia gravis cannot be predicted with sufficient certainty to make it possible to say that remission would not have taken place spontaneously in these patients.

In certain cases, at least, in which myasthenia gravis is associated with thymic tumor, the tumor is present before the onset of the symptoms of myasthenia gravis.

On the basis of this study, it would seem that roentgen irradiation of the thymus gland may be of value in treatment.

At present, no significant correlation can be made between the result obtained and the duration of the disease, the length of preoperative treatment with neostigmine or the histologic observations made in a study of the thymic tissue removed.

The problem of determining whether a thymus gland removed at operation is or is not hyperplastic is not a static one. Such designations must be considered tentative at this time.

A conclusive opinion as to the value of thymectomy in treatment of myasthenia gravis awaits the careful study of a larger number of cases over a longer period, and comparison of the course of the disease in the group of patients treated surgically with the course in a control group of patients receiving medical treatment only.

The Mayo Clinic.

CYSTICERCOSIS CEREBRI AND ITS OPERATIVE TREATMENT

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CYSTICERCOSIS cerebri is, unfortunately, a frequent disease in Poland. While almost unknown in the United States and considered as dying out in Western Europe, in Poland between 1921 and 1936 it accounted for about 0.29 per cent of all admissions to a large neurologic center. The inadequate control of the meat market and the lowering of the standard of hygiene and of the bodily resistance during the last war still further aggravated the situation. Thus, of the 1,879 patients admitted between 1936 and 1946 to the service of neurosurgery of the Neurologic Clinic in Warsaw, 23, or 1.22 per cent, had cerebral cysticercosis. That means that every eightieth patient was infested with Cysticercus cellulosae, the larva of Taenia solium.

The first observation on cysticercosis cerebri was made in 1588 by Rumler.[1] Paracelsus,[2] in 1650, noted epileptic convulsions occurring in the course of this disease (Henneberg,[3] 1936); yet it was only in the second half of the nineteenth and in the first years of the twentieth century that cerebral cysticercosis began to be extensively studied. Among the investigators were Virchow[4] (1860), Griesinger[5] (1862), Marchand[6] (1879 and 1881), Zenker[7] (1882), Sato[8] (1904), Wollen-

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berg [9] (1904), Henneberg [10] (1906 and 1936), Stern [11] (1907), Krause [12] (1911), Oppenheim [13] (1913), Opalski [14] (1931), Tyczka [15] (1935) and Bau-Prussakowa [16] (1937). However, these investigators were much more interested in the pathogenesis, histopathology and symptomatology of the disease than in its treatment, which was dismissed as more or less hopeless.

The present study is an attempt to classify cerebral cysticercosis with regard to the therapeutic indications and to review the results of surgical treatment obtained in 23 personal cases and 71 cases reported in the literature.

SYMPTOMS AND DIAGNOSIS OF CYSTICERCOSIS CEREBRI

It is now generally accepted that the diagnosis of cerebral cysticercosis presents great difficulties and is usually only tentative. For Wollenberg,[9] the variability of the clinical picture was pathognomonic of this condition. Stern [11] was of the same opinion. Bruns (1906) [11a] stated the opinion that the headache, vertigo, nausea and vomiting, appearing periodically, and chiefly after a rapid change in the position of the head, were indicative of a cysticercus lying free in the fourth ventricle. Oppenheim,[13] with the aid of this "symptom of Bruns," made an accurate diagnosis in several of his cases; however, he pointed out that his diagnosis in all cases was only tentative. Mintz [17] (1928) stressed the importance of fluctuations in the intracranial tension, symptoms of general toxemia, eosinophilia of the blood and transient hyperthermias. For Kulkow [18] (1931 and 1941), the eosinophilia of the blood and the cerebrospinal fluid and an increase in protein and lympho-

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17. Mintz, W.: Beitrag zur Chirurgie der Cysticercose des Grosshirns und des vierten Ventrikels, Deutsche Ztschr. f. Chir. **209**:104, 1928.

18. Kulkow, A.: Ueber die vitale Diagnostik des cerebralen Cysticercus im Zusammenhang mit Veränderung im Liquor cerebrospinalis, J. nepropat. i psikhiat. **23**:82, 1930; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **59**:613, 1931; Zur Symptomatologie und Diagnose der Hirncysticercose, ibid. **172**:643, 1941.

cytes in the latter presented the chief elements of diagnosis. Pfeiffer [19] (1907) was helped in diagnosis by puncturing the brain and withdrawing through the needle a portion of the capsule of the parasitic cyst. Demonstration of these cysts in the subcutaneous tissue (Bourquet and Merat,[20] 1927; Grzybowski and B. Stepien,[21] 1932) and in the eye (Poggio, cited by Oppenheim [13]); of the giant cells of Langhans in the cerebrospinal fluid (Opalski [14]), and, finally, of the presence of multiple small areas of calcification within the skull, makes a diagnosis of cysticercosis cerebri most probable, while demonstration in the cerebrospinal fluid of a whole parasite (Morawiecka,[22] 1928) or of a portion of one (Hartman, cited by Oppenheim [13]) makes it certain. For the diagnosis of cysticercosis of the posteriorcranial fossa, Arana and Asenjo [23] (1945) stated that the following roentgenographic signs were valuable: symmetric dilatation of the ventricular system and partial obliteration of the aqueduct of Sylvius and the fourth ventricle, with presence of air in both and in the cisterna magna.

The chief difficulty in reaching a correct diagnosis in a case of cerebral cysticercosis is the variability of the clinical picture, which is dependent on the number of parasites, the stage of their development, their location, the pathologic change they cause in the brain and, finally, the individual susceptibility of the patient. In general, the clinical picture, which often changes in the same patient with the stage of the disease, consists in focal symptoms and those of a chronic, diffuse inflammatory lesion of the brain.

Because of this confusing wealth of symptoms in cases of cerebral cysticercosis, several attempts have been made to classify the cases. Griesinger [5] classified them according to the most characteristic symptoms; Sato [8] preferred to subdivide the cases, according to the location of the parasitic cysts. Henneberg,[10] Schmitz [24] (1928) and Margulis [25]

19. Pfeifer: Cysticercus cerebri mit dem klinischen Bilde einer korticalen sensorischen Aphasie, durch Hirnpunktion diagnostiziert und operiert, Neurol. Zentralbl. **20**:969, 1907.

20. Bourquet and Merat: Cysticercose multiple avec kyste cérébral provoquant depuis dix ans de l'epilepsie jacksonienne: Ablation au niveau du pied de la II-e frontale; Siège confirme par la faradisation céntrale, Arch. internat. de laryng. **6**:1072, 1927; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **49**:416, 1928.

21. Grzybowski, M., and Stepien, B.: Cysticercosis of the Meninges and the Skin (Polish), Przegl. dermat. **26**:3, 1931.

22. Morawiecka, J.: Cysticercosis of the Cauda Equina, Neurol. Polska **11**: 314, 1928.

23. Arana, R., and Asenjo, A.: Ventriculographic Diagnosis of Cysticercosis of the Posterior Fossa, J. Neurosurg. **2**:181, 1945.

24. Schmitz, F.: Ueber einen Fall von Gehirncysticercose, Med. Klin. **24**:894, 1928.

25. Margulis, 1933, cited by Bau-Prussakowa.[16]

(1933) accepted Griesinger's classification, decreasing only the number of groups. Tyczka [15] and Bau-Prussakowa [16] divided their cases according to localization and the leading symptom complex.

Our classification, both of our own cases and of those collected from the literature, is based on the nature of the pathologic changes induced by the parasitic cysts. These changes, in turn, produce a more or less distinct clinical picture.

Group 1 comprises the cases in which the cysts, oftenest single, cause, by destruction or irritation of the brain, symptoms similar to a cerebral tumor. The symptoms in this group depend on the area involved. To group 2 belong the cases in which the cysts, which are usually numerous, produce swelling of the brain and symptoms of a diffuse cerebral lesion, and in group 3 the cases are those in which the parasites cause chiefly hydrocephalus internus, with its more or less characteristic symptomatology.

The clinical picture of group 1 consists, therefore, of symptoms of a focal lesion of the brain and those of intracranial hypertension. In cases of group 2, the leading syndrome consists of symptoms of increased intracranial tension and signs of psychic disturbance. The changes in the blood and the cerebrospinal fluid, characteristic of cysticercosis, i.e., eosinophilia, increase in protein and lymphocytosis, are observed in nearly every case in this group. The symptoms seem to result chiefly from severe edema of the brain, which was encountered in each of the patients at operation. Cysticercosis in children usually produces the pathologic and clinical picture characteristic of group 2, the disease as a rule following a very stormy course. This is probably due to a special susceptibility of children to the toxic action of the parasites. In group 3, the clinical picture seems to result from internal hydrocephalus, which follows obliteration of the channels of the cerebrospinal fluid by the parasites. A combination of symptoms of intracranial hypertension and atypical and variable focal symptoms characterizes these cases.

Of course, oftener than not, it is impossible to classify the case correctly. One case, belonging apparently to group 1, may present signs of mental disturbance, while focal symptoms may be found in a patient whose clinical picture has all the characteristics of group 2, or, oftener of group 3. However, such "foreign" symptoms are not, as a rule, major ones and should not be misleading. After all, what is important in diagnosis is not this or that symptom, but the whole clinical picture; not the detail, but the *ensemble*. The borderlines of the various groups being rather hazy, the value of this classification, as of all others, is controversial. We feel that the grouping of cases of cerebral cysticercosis has some usefulness in diagnosis, in prognosis and, especially, in facilitation of the choice of the operative procedure.

GROUP 1.—Cysticercosis cerebri, the symptoms of which are similar to those of any other tumor of the brain, were represented in our own series by 11 cases (47.8 per cent) and of the cases recorded in the literature by 52 (73.2 per cent), or by a total of 63 cases, that is, by 67 per cent of the 94 cases in which surgical treatment was employed.

The symptoms depend, of course, on the number of parasites and on their location. There are, however, three clinical pictures which are more often encountered than others, namely, those of a lesion of a cerebral hemisphere, of involvement of the fourth ventricle and of a lesion in the region of the optic chiasm.

The following observations will illustrate the three clinical pictures.

CASE 1.—*Cysticercosis producing focal epileptic seizures.*

W. P., a woman aged 31, was admitted on Aug. 2, 1945. Since June 1943 she had suffered from headaches, which had increased steadily in severity. Since December 1944 she had had nausea and vomiting, which had relieved the headaches for a little while. During attacks of severe headache there had been transient dimness of vision. Since January 1945 she had had epileptic seizures. These started with a feeling of general weakness and a sensation of constriction of the throat; after that, there were deviation of the angle of the mouth to the left, tonic spasm, rotation, clonic movements of he left upper extremity and then of the left lower extremity and, finally, loss of consciousness. The attacks lasted about twenty minutes. At first, the patient had them every four to five weeks, but just prior to her admission to the hospital they had been occurring every few days, or even several times a day. Since July 1945, in addition to the attacks already described, she had had three seizures characterized by numbness of the entire right side of the body. She admitted to having eaten raw meat.

Neurologic examination gave essentially normal results except for bilateral papilledema of 3.0 and 5.0 D., respectively, with hemorrhages. The cerebrospinal fluid was under high pressure and contained 0.99 per cent protein and 43 lymphocytes per cubic millimeter. Reactions for globulin were positive. Examination of the blood and urine and roentgenograms of the skull revealed nothing abnormal.

With a tentative diagnosis of cerebral cysticercosis, chiefly in the right motor region of the brain, operation was performed on August 13. After the cortex had been exposed through an osteoplastic craniotomy over the motor and temporal regions, seven cysticerci, located just beneath the leptomeninges in the precentral region, were encountered. They appeared as small, white or yellow spots or nodules, lying close to the blood vessels, oftenest in an angle between a large artery and its branches. After the leptomeninges had been incised around the parasites, the cysts were dissected free with a blunt instrument and enucleated. The postoperative course was uneventful, and the patient left the hospital on August 30, seventeen days after operation, free of headaches and epileptic seizures. She was forwarned, however, that probably she had a similar lesion in the left cerebral hemisphere and that she should be ready for another operation if similar attacks appeared in her right extremities.

For several weeks the patient felt perfectly well; she then began to complain of attacks of the following nature: First she experienced numbness of the fingers of her right hand and then of the whole upper extremity, which soon became stiff; she lost consciousness, and finally clonic movements appeared in the right upper extremity. Returning every two or three days, they lasted ten

minutes and were followed by severe headaches and somnolence. Since the first attack, the right upper extremity had become somewhat weaker. When the patient was readmitted, on Nov. 7, 1945, she showed bilateral secondary atrophy of the optic nerve, most pronounced on the right; dilatation of the left pupil; slight paresis of the lower portion of the right facial nerve and the right hand, and exaggeration of the tendon reflexes on the right side. A second operation was performed on November 13, with the diagnosis of cysticercosis in the left motor region of the brain. This time, only two cysts were exposed, in the motor and temporal regions, and they were enucleated in the same way as before. The patient withstood the operation well and was discharged to her home on December 15, without any neurologic symptoms. At the time of this report, one year after operation, she stated that she is well and without attacks.

Comment.—Before her first operation, the patient had had two kinds of attacks, the one consisting of clonic movements in both extremities on the left side, with loss of consciousness; the second characterized by attacks of numbness of the whole right side of the body. There was no doubt, therefore, that she had lesions in both cerebral hemispheres, causing symptoms of excitation rather than of paralysis of the cortex. In addition, she had had symptoms of intracranial hypertension, and examination of the cerebrospinal fluid showed lymphocytosis, increased protein and a positive reaction for globulin. It was thought, therefore, that the lesion must be of parasitic origin. She also admitted to having eaten raw meat; so she had had an opportunity to become infected with T. solium. The first operation confirmed our tentative diagnosis, and the appearance of seizures in the right upper extremity was a foreseen result of the presence of parasities also in the left cerebral hemisphere.

A similar observation was reported by Sejnson,[26] Bulgaris,[27] Henneberg,[3] Penfield and Erickson[28] (1941), all of whom pointed out that convulsions constitute the commonest symptom of invasion of the brain by Cysticercus cellulosae.

The cerebral hemisphere is the most frequent site of the cysticerci, being noted in 60.3 per cent of all cases of group 1. Epileptic seizures, as a symptom of cysticercosis of the cerebral hemispheres, is second only to the signs of intracranial hypertension. They were observed in 24 of 63 cases. In 13 cases the seizures were generalized, and in 11 they were of the jacksonian type. Of the cranial nerves, the facial was the most frequently involved. It was found to be paretic in 9 cases, in all of which the paresis was of central origin. Anisocoria was observed in only 2 cases, paresis of the upward gaze and of the abducens nerve in

26. Sejnson, M.: Zur Kasuistik des Grosshirncysticercus, Zentralbl. f. sov. Chir. **4**:1521, 1929; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **56**:527, 1930.

27. Bulgaris: Ueber einen Fall von Gehirncyst (1926), cited by Henneberg.[3]

28. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941.

1 case, weakness of the extremities in 10 cases and paralysis in 4 cases. Aphasia was noted in 6 cases; in 4 cases it was motor and in 2 sensory. Psychic disturbances were observed in only 6 of the 63 cases. They consisted in impairment of memory, states of anxiety and disorientation in time and space. The duration of the disease in this group of cases was from seven weeks to ten years.

Case 2.—*Cysticercosis producing symptoms of a cerebellar lesion.*

L. G., a woman aged 35, was admitted on May 4, 1943. Since 1940 she had suffered from headaches, which for the last six months had been accompanied with nausea and vomiting. Since November 1942 she had had difficulty in walking because of staggering to either side, especially to the left. For two months her eyesight had been growing steadily weaker, and on looking to the right she saw double.

Neurologic examination showed choked disks of 3.0 and 4.0 D., respectively, with hemorrhages, horizontal nystagmus on her looking to the left, hypotonia of the right extremities and ataxia of the left upper extremity. While walking, she staggered to the left; when examined for Romberg's sign, she fell to the same side. The roentgenograms of the skull showed conspicuous thinning of the convolutions. Examination of the blood showed normal constituents.

With the diagnosis of tumor in the posterior cranial fossa, operation was performed on May 20. A conventional suboccipital craniectomy was carried out. The cisterna magna was observed to be large and contained a great quantity of cerebrospinal fluid. When the cerebellar tonsils were pushed apart, a large, semitranslucent cyst was seen to occupy the fourth ventricle completely. During its removal the cyst ruptured; thereafter it was easily dissected free and cut off from the choroid plexus, to which it was adherent. The ventricular wall was covered with a whitish, granular tissue. Microscopic examination of the wall of the cyst confirmed our supposition of Cysticercus cellulosae. The postoperative course was smooth, and the patient left the hospital on June 6, seventeen days after operation, free of any neurologic disturbance. When seen three years later, she was completely well and able to work.

Comment.—In this case, also, symptoms of increased intracranial tension were accompanied with signs of localizing value. Our pathologic diagnosis, however, was incorrect. There was no past history of infection with Taenia solium, and no eosinophilia of the blood; therefore, we had none of the elements necessary for a correct pathologic diagnosis. Neither in this case, nor in several others, did we observe the sign of Bruns, which for Oppenheim [18] was pathognomonic of cysticercosis of the fourth ventricle. The postoperative course in this case was uneventful, in spite of the contents of the ruptured parasite coming into contact with the wall of the fourth ventricle. Such an occurrence is generally dreaded. Verco [29] (1889), in a case of purulent meningitis following removal of a cysticercus, referred the infection to the organism liberated from the

29. Verco, J.: Hydatid of the Brain, Removal by Operation, Death After Four Days, Neurol. Zentralbl. **9**:443, 1890.

parasitic cyst. According to Mehlhouse, as cited by Henneberg,[3] these cysts are not always sterile, but at times contain organisms, which cause, on the one hand, the death of the parasite, and, on the other, a chronic inflammatory process around the cyst. However it may be, of the 94 cases of cerebral cysticercosis, 23 cases of our own and 71 cases reported by others, only 7 were of purulent meningitis following operation. It seems, therefore, that the fear of infection of the brain and meninges by organisms liberated from the parasitic cysts has little, or no, foundation. Even in such cases as the one just described, in which the contents of a cyst came into contact with the cerebrospinal fluid pathways, the postoperative course may be smooth.

The posterior cranial fossa was the site of cysticercosis in 14 cases, that is, in 22.2 per cent of the reported cases of group 1. The parasites were located in the fourth ventricle in 11 instances, both in the fourth ventricle and at the base of the brain in 2 cases and in the region of the acoustic nerve in 1 case. Symptoms of intracranial hypertension were present in all cases. Choked disks were observed in 10 cases, and secondary optic nerve atrophy occurred in 3 cases. Involvement of the trigeminal and abducens nerves was found in 1 case and of the vagus nerve also in 1 case. Diminution of hearing and paresis of the hypoglossus nerve occured in 2 cases; anisocoria in 2 cases and nystagmus in 6 cases. Disturbances in station and walking were definite in 8 cases, and ataxia of the extremities was noted in 3 cases. The average duration of the disease, when the cysticerci invaded the posterior cranial fossa, was from two to three years; the shortest period was six months, and the longest, ten years.

CASE 3.—*Cysticercosis producing hypothalamic and thalamic symptoms.*

H. K., a woman aged 41, was admitted on April 5, 1940. In December 1938, she had an attack of "flu," lasting four weeks, with a temperature of 39 C. (102.2 F.). Since January 1939, she had suffered from attacks of the following character: For six to eight hours she felt badly and experienced nausea and vomiting, followed by headaches; she then had a burning sensation in the face and the upper extremities, accompanied with hyperhydrosis of the hands and forearms; at the same time, she complained of sensations of cold in her lower extremities, which were covered with "goose flesh"; after several minutes of this double sensation, she felt numbness, followed by tearing and stabbing pains, in her lower extremities. These attacks occurred every three to four days and lasted for several hours. In September 1939, three of these attacks were accompanied with numbness of the right half of the face, lasting for twelve hours. In March 1940 she noticed that the slightest touching of her hair was apt to increase the headaches. She felt then as though she "were touching a tooth nerve." Sometimes, when putting her head on a pillow, she felt as though she was putting it on ice. Indeed, the mere thought of cold was likely to increase the sensation of cold she felt in her lower extremities during the attacks. The hypersensitivity to sensory stimuli was not always present, but appeared usually with the attacks which have already been described. On

three occasions these attacks were followed by loss of consciousness. One week prior to her admission she had had an attack of a similar kind, without loss of consciousness but complicated by numbness and torsion of the fingers of both hands; that attack lasted about half an hour. An aunt of the patient had been subject to generalized convulsions.

Physical examination showed thoracic scoliosis, dating from the age of 6 years; choked disk on the right; blurring of the temporal edges of the left nerve head, and exaggeration of the tendon reflexes on the left side. The roentgenograms of the skull revealed distention of the sella turcica with destruction of its dorsum. The blood and urine were normal.

On April 15, 1940, ventriculographic examination was carried out, the roentgenograms showing dilatation of both the lateral ventricles and the third ventricle. No air was seen in the aqueduct of Sylvius or in the fourth ventricle. Below and slightly anterior to the recessus suprapinealis of the third ventricle, a quadrangular area of calcification was visible in the lateral ventriculograms.

A tentative diagnosis of calcified cysticercus or tuberculoma in the posterior part of the third ventricle was made and palliative treatment, in the form of the procedure of Stookey, was thought advisable. The skull was opened in the right frontal region and the perichiasmic region was exposed. The right optic nerve was observed to be covered with a small cysticercus, while a second cyst was located between that nerve and the internal carotid artery. Four others were observed in the cisterna chiasmatis. All six cysts were removed without difficulty, and the very thin lamina terminalis was then ruptured. Unfortunately, the calcified lesion, in front of the entrance to the aqueduct of Sylvius, could not be seen clearly. The procedure, therefore, was discontinued and the skull was closed. The patient withstood the operation well and left the hospital on May 4, nineteen days after operation, without complaints. Four years later she reported that she was well and without her previous attacks.

Comment.—For fifteen months previous to admission and operation, the patient had had peculiar attacks, coming every three to four days and almost always of the following pattern: An aura, lasting six to eight hours, was characterized by general malaise, nausea, vomiting and headaches, which on several occasions were increased by mere touching of the hair. The aura was followed by a burning sensation in the face and in the upper extremities, accompanied with profuse sweating of the hands and forearms, while the feet felt cold and the lower extremities were covered by "goose flesh." Sometimes the mere thought of cold increased the sensation of cold in the feet. Finally, she felt numbness in both feet and then stabbing and tearing pains in both lower extremities. These attacks lasted several hours. The severer attacks were followed by loss of consciousness, and three attacks were accompanied with numbness of the right side of the face.

These unusual attacks are certainly akin to those observed in the diencephalic epilepsy of Penfield,[30] (1929), and perhaps even more akin

30. Penfield, W.: Diencephalic Autonomic Epilepsy, Arch. Neurol. & Psychiat. **22**:358 (Aug.) 1929.

to the subthalamic attacks of Engel and Aring [31] (1945). In our case, they seemed to be of thalamohypothalamic nature and were presumably caused by the mechanical and toxic action of the parasites on the thalamus and the hypothalamic nuclei. Or, they may have been an expression of an acute and transient obstruction of the cerebrospinal fluid pathways, producing transient hypertension within the third ventricle (Sjöqvist,[32] 1941). However it may be, the fact remains that once the cysticerci were removed the attacks disappeared and had not returned four years after operation.

Our own series contains 2 more observations on cases in which parasitic cysts were located in the perichiasmic region. In 1 case the clinical picture was that of a glioma of the optic nerve, and in the other, that of chronic hydrocephalus internus. Ritchie, French and Titrud [33] (1945) also observed a case in which the cysticercus was located in the region of the optic chiasm.

Group 2.—To group 2 belong the cases in which the cysticerci produce swelling of the brain. In our series, there were 5 such cases, whereas of the 71 reported in the literature only 2 seem to belong to this group. The difference in the frequency of cases of this type in the two series is presumably due to the fact that our series comprises all types of cerebral cysticercosis whereas the cases reported in the literature are more or less selected, comprising mainly cysticercosis producing the clinical picture of cerebral tumor.

The leading symptom complex in group 2 is that of intracranial hypertension and mental disturbance. The symptoms of localizing value are infrequent and, when present, are kept in the background by other signs.

Headache, nausea and vomiting were observed in all cases. Papilledema, of from 1.5 to 3.0 D., was present in 6 of 7 cases, with retinal hemorrhages in 2 cases. In 1 case in which vision was very poor, secondary optic nerve atrophy was found. One of the patients with papilledema of only 3.0 D. was completely blind, his loss of vision having developed rapidly. Most probably, his condition was not true papilledema, but neuritis optica, which, as is well known, is often difficult to differentiate from choked disk resulting from increased intracranial pressure. The rapid loss of vision is, however, not a characteristic element of the cases of group 2 alone, but is also encountered in cases of group 3. Psychic disturbances were observed in all the cases of group 2. They usually consisted of psychomotor agitation, visual and

31. Engel, G. L., and Aring, C. D.: Hypothalamic Attacks with Thalamic Lesion, Arch. Neurol, & Psychiat. **54**:37 (July) 1945.

32. Sjöqvist, O.: Hypothalamic Discharge and Its Relation to Epilepsy, Acta chir. Scandinav. **85**:235, 1941.

33. Ritchie, W. P.; French, L. A., and Titrud, L. A.: Cysticercosis: A Case Report, J. Neurosurg. **2**:543, 1945.

auditory hallucinations, confusion, impairment of memory, euphoria or slowing of mental processes. Of the symptoms of some localizing value, nystagmus and paresis of the lower part of the facial nerve were observed in only 2 cases, while unilateral corneal areflexia and paresis of the abducens nerve were each found in only 1 case. The duration of the disease was never longer than a few months. The age of the patients ranged from 10 to 45 years. Our 2 cases of cysticercosis cerebri in children belong to this group. In both cases the disease ran a severe course, being characterized by marked mental disturbance and loss, or weakness, of vision. It seems that the brain in children is unusually susceptible to the presence of parasites and that it reacts with severe edema.

The following case occurred in our personal observation.

CASE 4.—*Cysticercosis producing rapid loss of vision and psychic disturbances.*

B. S., a boy aged 13, was admitted on Aug. 4, 1945. Since January 1945 he had had headaches, nausea and vomiting, and for two weeks prior to admission he had complained of rapid loss of vision. Four days before being admitted to the hospital he became completely blind. For two weeks the boy had been confused and agitated and had had visual and auditory hallucinations.

Neurologic examination showed bilateral blindness, although the papilledema was only 3.0 D. The right pupil was larger than the left, and there was paresis of the lower portion of the left facial nerve. The patient was confused and agitated, could not be kept in bed, was untidy, saw soldiers with guns and grenades and heard voices. The pressure of the cerebrospinal fluid was high. It contained 0.99 per cent of protein and 19 lymphocytes per cubic millimeter. The blood showed 7 per cent eosinophils.

In view of the general clinical picture, there was no doubt that the diagnosis was cysticercosis cerebri and that the infection of the brain with the larvae was diffuse. However, having at hand a symptom of localizing value, namely, the paresis of the lower portion of the facial nerve, we thought it advisable to expose the right frontal lobe, expecting to find there at least some of the cysticerci. When, on August 9, the very swollen brain was exposed in the right frontal region through an osteoplastic craniotomy, five parasitic cysts were observed in the precentral region, just beneath the leptomeninges. They were all removed. Another parasitic cyst was then exposed and removed from the cisterna chiasmatis, which was explored because of the rapid loss of vision. However, the optic nerves were observed to be macroscopically normal.

The postoperative course was at first rather stormy, the boy being confused and agitated; however, with time he became quieter, and finally the confusion cleared completely. He left the hospital on August 31. His eyesight, however, did not return, and the boy was still blind when seen ten months later. Except for the blindness, he was entirely well.

Comment.—The symptoms, consisting of intracranial hypertension, psychic disturbances and eosinophilia (7 per cent), made the diagnosis certain in this case. The paresis of the lower portion of the left facial nerve helped us to localize at least some of the parasitic cysts, which probably were numerous, increased intracranial tension, in our opinion,

being almost pathognomonic of a lesion of the frontal lobe (Rudowski,[34] 1946).

In this case, as in all similar cases, the brain, when exposed at operation, was found to be edematous. The cause of such extreme swelling of the brain is, of course, hard to determine. Perhaps it is caused by the action of toxins present in the parasitic cysts. According to Bulgaris,[27] MacArthur [35] (1935) and Henneberg,[3] the living parasites do not produce any toxins and, for that reason, do not produce any clinical symptoms; however, according to these authors, a dead parasite is very toxic and is responsible for all the symptoms of the disease.

As already mentioned, rapid loss of vision is of frequent occurrence in group 2, being, however, observed also in cases of group 3. A case of temporary blindness in a patient with cerebral cysticercosis was described by Marchand.[6] Brecke, as cited by Henneberg,[3] reported sudden blindness in a patient with papilledema and retinal hemorrhages. Maragliano [36] (1904) stated the belief that in his case the bilateral optic neuritis, which was observed in the beginning of the disease, changed later into papilledema, while Wollenberg [9] and Strebel [37] (1922) stated that in their patients neuritis optica led finally to optic nerve atrophy. In our opinion, the blindness frequently observed in cases of cerebral cysticercosis probably results from an inflammatory process of the optic nerves combined with choking of the disks produced by intracranial hypertension.

Group 3.—The cases of cysticercosis cerebri belonging to group 3 are characterized by internal hydrocephalus, resulting from chronic leptomeningitis, especially at the base of the brain, and/or chronic ependymitis, produced by parasitic cysts. We include here the 7 cases (30.4 per cent) in our series and the 17 cases (23.9 per cent) reported by others. The clinical picture is here made up mainly of symptoms of increased intracranial pressure and of some focal signs which are atypical and variable, still more so than in cases of group 2. Signs of psychic disturbance are also encountered. Because of great difficulty in making any definite diagnosis, ventriculography is in this group of cases a necessity and then, in the majority of cases, shows only that the patient has hydrocephalus.

Headache was noted in all our cases and in 15 cases from the reports of others. Nausea and vomiting were observed in 16 cases and choked disk in 18 cases, while in 3 cases the papilledema was changing into

34. Rudowski, W.: On Diagnosis of Frontal Lobe Tumours, 1946, to be published.

35. MacArthur, W.: Cysticercosis of the Brain, Brit. M. J. **2**:1229, 1935; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **79**:546, 1936.

36. Maragliano, D.: Cysticerque du cerveau, cited by Krause.[12]

37. Strebel, 1922, cited by Henneberg.[3]

optic nerve atrophy. Although in 1 of our cases there was papilledema of 10 D., eyesight was almost normal. Signs of mental disturbance, which were here not so conspicuous as in cases of group 2, were encountered in 6 of our own cases and in 2 cases reported by others. In 3 instances they consisted of impairment of memory; in 2, of disorientation in time, space and situation, and in the 3 others, in agitation and a transient state of confusion and anxiety. In 4 cases there was paresis of the facial nerve of central origin; in 2 cases, anisocoria, and in 1 case each, paresis of the fifth, sixth and eighth cranial nerves. Disturbance of equilibrium was seen in 8 cases, exaggeration of tendon reflexes in 3 cases, tremor of all extremities in 2 cases and tremor of both hands in 1 case. Paresis of one of the extremities was observed in 1 case. Changes in the cerebrospinal fluid, consisting of increased protein content (of from 0.6 to 3.0 per cent), lymphocytosis (of from 6 to 80 cells per cubic millimeter) and positive reactions for globulin, were encountered in only half the cases. Ventriculography was carried out in 5 of our cases and in 16 reported in the literature, revealing dilatation of the whole of the ventricular system in all instances. It may be added that we had never seen such degrees of dilatation of the ventricular system as in these cases, this condition being due most probably to the slowness with which the basal leptomeningitis and the ependymitis produce the obliteration of the cerebrospinal fluid pathways.

The following case illustrates this group.

CASE 5.—*Multiple cysticerci producing widespread involvement of the cerebrum.*

B. S., a man aged 39, was admitted on Aug. 25, 1943. Headaches, accompanied with nausea and vomiting, appeared in April 1943. In May he had an episode of motor aphasia, lasting two hours; then, after two weeks, aphasia reappeared, with a duration of twelve hours. Since the beginning of the disease he had noticed impairment of memory and diminution of vision in his right eye.

Neurologic examination revealed apathy and somnolence, with impairment of memory, showing bilateral papilledema of 3.0 and 5.0 D. with retinal hemorrhages. Visual acuity was 6/9 in the right eye and was normal in the left eye. The left pupil was larger than the right, and there was paresis of the lower portion of the right facial nerve.

Ventriculography, carried out on Sept. 1, 1943, revealed dilatation of the lateral and the third ventricles, no air being found in the aqueduct of Sylvius or in the fourth ventricle. Since we were unable to make an accurate diagnosis, a palliative treatment, following the procedure of Stookey, was decided on and carried out on September 1. The brain was exposed through an osteoplastic craniotomy in the right frontal region. The leptomeninges, forming the cisterna chiasmatis, were thick and opaque. Inside the cistern, several small cysticerci were brought into view and removed by suction. The optic nerves were freed from dense adhesions, and then the Stookey operation was performed. For a few days after the operation the patient was agitated; he then became somnolent and showed considerable impairment of memory. Gradually, however, he improved and left the hospital on September 29, four weeks after operation, entirely well.

Comment.—The parasites removed from the perichiasmatic cistern were certainly not the only ones present in this patient's brain. We did not belittle the importance of the two episodes of motor aphasia, due certainly to cysticerci located in the region of the third frontal convolution; before the operation, however, we could not be sure of their real cause. On the other hand, a lesion located here could not be responsible for dilatation of the lateral and the third ventricles; in view of the serious condition of the patient, therefore, the palliative treatment for hydrocephalus seemed to be indicated. Other cysticerci were probably located in the aqueduct of Sylvius, in the fourth ventricle or in the other basal cisterns.

The diagnosis of cysticercosis of the brain is usually difficult, and often impossible. In the cases in group 1, an accurate pathologic diagnosis can be made only by demonstration of parasitic cysts in the subcutaneous tissue, the muscles, the eyes or other structures, by the finding of eosinophilia of the blood and/or the cerebrospinal fluid, and, finally, by roentgenologic demonstration of typical carrot, or dunce's cap, areas of calcification in the brain. Of the 11 personal cases belonging to this group, an accurate diagnosis was made in only 2 instances (cases 5 and 11). A correct diagnosis in cases of group 2 is somewhat easier to make, since they present a rather clearcut clinical picture, consisting of symptoms of intracranial hypertension and psychic disturbances, with visual and auditory hallucinations. The diagnosis here is also certain only when these symptoms are associated with eosinophilia of the blood or lymphocytosis of the cerebrospinal fluid, with increased protein and a positive reaction for globulin. Of the 5 personal cases belonging to this group, an accurate diagnosis was made in 3 instances. Of the 7 cases included in group 3, it was possible to make a correct diagnosis in only 2. In 1 case we were aided by the presence of a calcified area inside the skull, eosinophilia of the blood and changes in the cerebrospinal fluid, whereas in the other the patient's past history of infection with T. solium was of diagnostic aid.

In summary, we were able to make an accurate diagnosis of cerebral cysticercosis in only 7 of our 23 cases, that is, in one third of the cases. Of the cases reported in the literature, a correct diagnosis was made in only 8 of 71 cases, or 11.2 per cent.

RESULTS OF OPERATIVE TREATMENT OF CYSTICERCOSIS CEREBRI

Verco [20] was apparently the first to remove a cysticercus from the brain. However, the patient died of purulent meningitis four days after operation. Maydl [38] (1899) enucleated a parasitic cyst from the right

38. Maydl, K.: Un cas d'épilepsie partielle causée par un cysticercus: Operation. Guerison, Sociéte des med. Tcheques de Prague, Nov. 27, 1899; abstracted, Neurol. Zentralbl. **25**:33, 1906.

motor region of the brain. The patient felt well for about four years; then jacksonian seizures reappeared and a second operation was necessary. After the extirpation of another cysticercus the recovery was permanent. After that, reports on operative treatment of cysticercosis cerebri began to appear more frequently; yet Oppenheim [13] pronounced himself against surgical treatment of the lesions, on the grounds that the operation is dangerous and more or less hopeless. The same opinion was expressed by Krause (1923), who, in discussing a case reported by Borchardt,[39] stated that all his patients died a few weeks or a few months after operation of basilar meningitis. However, between 1923 and 1935 there were on record 46 cases in which cysticercosis cerebri was treated surgically, with the following results: cure in 9 cases and improvement in 18 cases, with death in only 9 cases. In spite of these encouraging results, Tyczka [15] urged against operative treatment, being of the opinion that the "infrequent attempts of surgical removal of the parasitic cysts nearly always ended unsuccessfully." Also, Dandy [40] (1938) expressed the opinion that "surgical treatment [of cysticercosis] is of no avail."

While the individual reports on the operative treatment encountered in the literature are based generally on 1 or 2 observations, our own series comprise 23 consecutive cases.

In the 71 observations published by others, the operative procedures and the results obtained were as follows: In 52 cases of group 1, 56 operations were carried out, including 43 osteoplastic craniotomies, 11 suboccipital craniectomies, and 2 subtemporal decompressions. Of the 2 cases belonging to group 2, an osteoplastic craniotomy was done in 1 and a suboccipital craniectomy in the other, whereas of the 17 cases of group 3, a suboccipital craniectomy was done in 16 and an osteoplastic craniotomy in 1. All in all, for the 71 cases, there was a total of 75 operations. In 24 cases of supratentorial cysticercosis, one parasitic cyst was removed; in 3 cases, two cysts were removed, and in 15 cases multiple cysts were encountered and removed. In 1 case a Cysticercus racemosus was extirpated, and in 2 cases the cysts could not be removed. In 28 cases the cystercerci were located infratentorially. In 11 instances they were removed from the fourth ventricle (in 10 cases a single cyst, and in 1 case multiple cysts), in 11 cases from the base of the skull and in 1 case from the cerebellum; in 5 cases the operation consisted only of decompression, the cysticercosis being inoperable.

In our own series, in the 11 cases belonging to group 1, 12 operations were carried out (9 osteoplastic craniotomies and 3 suboccipital

39. Borchardt, M.: Cysticercus cerebri, Zentralbl. f. Chir. **7**:278, 1924.
40. Dandy, W. E.: Hirnchirurgie, Leipzig, Johann Ambrosius Barth, 1938.

craniectomies). In the 5 cases of group 2, 7 operations were performed (3 osteoplastic craniotomies, 3 subtemporal decompressions and 1 suboccipital craniectomy). In the 7 cases belonging to group 3, 4 osteoplastic craniotomies, 2 suboccipital craniectomies and 1 subtemporal decompression were performed. All in all, in our 23 cases, 26 operations were performed. The parasitic cysts were removed in 16 instances; in 5 cases the operation had only a palliative character; in 4 cases the procedure of Stookey was followed, and in 1 case cerebellar decompression was performed.

In table 1 the number and the location of the parasitic cysts removed are presented. In 9 instances, they were encountered on the surface

TABLE 1.—*Location and Number of Cysticerci Removed in Authors' Personal Cases*

Location	Single	Multiple	Total
Cortex	2	7	9
Chiasmic region	1	2	3
Fourth ventricle	2	..	2
Fourth ventricle and base of the skull	1	..	1
Close to eighth nerve	1	..	1
Total	7	9	16

TABLE 2.—*Results of Operative Treatment in 71 Cases Reported in the Literature*

Group	1	2	3	Total
Recovery	13 (25 %)	.....	1 (5.9%)	14 (19.7%)
Improvement	20 (38.4%)	.....	1 (5.9%)	21 (29.6%)
No change	3 (5.8%)	.....	4 (23.5%)	7 (9.9%)
Patient dead	10 (19.2%)	2 (100%)	11 (64.7%)	23 (32.4%)
Fate unknown	6 (11.6%)	.....	.....	6 (8.4%)
Total	52 (100 %)	2 (100%)	17 (100 %)	71 (100 %)

of the cortex; in 3, in the region of the optic chiasm; in 2, inside the fourth ventricle; in 1, both in the fourth ventricle and beneath one of the cerebellar tonsils, and in 1, close to the acoustic nerve. In 7 cases the cysts were single; in 7 cases their number ranged from two to six, while in 2 cases we removed thirteen and thirty cysts, respectively. The size of the parasites ranged from that of a pea to that of a large plum.

Table 2 gives a summary of the results obtained by other authors: Of the 52 cases of group 1, recovery occurred in 13 (25.0 per cent), improvement in 20 (38.4 per cent), no improvement in 3 (5.8 per cent), and death in 10 cases (19.2 per cent). Nothing is known about the fate of 6 patients. In both cases belonging to group 2 the outcome

was fatal. Of the 17 cases of group 3, recovery followed in 1 case (5.9 per cent), improvement in 1 case and no change in 4 cases (23.5 per cent); in 11 cases (64.7 per cent) the patient died. Therefore, of the 71 patients, 23 died, the case mortality being 32.4 per cent and the operative mortality 32 per cent. Three patients died of paralysis of the respiratory center; 4, of meningitis; 1, of pneumonia; 1, of influenza, and for 14 patients no cause of death was given.

Our own results are presented in table 3. Of the 11 patients belonging to group 1, 4 (36.3 per cent) recovered, 4 (36.3 per cent) improved, in 1 (9.2 per cent) no improvement was noted and 2 (18.2 per cent) died. Of the 5 cases in group 2, 2 (40.0 per cent) improved, 1 showed

TABLE 3.—*Results of Operative Treatment in 23 Personal Cases*

Group	1	2	3	Total
Recovery	4 (36.3%)	.....	.....	4 (17.3%)
Improvement	4 (36.3%)	2 (40%)	2 (28.5%)	8 (34.8%)
No change	1 (9.2%)	1 (20%)	.....	2 (8.8%)
Patient dead	2 (18.2%)	2 (40%)	5 (71.5%)	9 (39.1%)
Total	11 (100 %)	5 (100%)	7 (100 %)	23 (100 %)

TABLE 4.—*Results of Operative Treatment in 94 Cases of Cysticercosi Cerebri Treated Surgically*

Group	1	2	3	Total
Recovery	17 (26.9%)	.....	1 (4.2%)	18 (19.1%)
Improvement	24 (38.1%)	2 (28.6%)	3 (12.5%)	29 (30.9%)
No change	4 (6.3%)	1 (14.3%)	4 (16.6%)	9 (9.6%)
Patient dead	12 (19.0%)	4 (57.1%)	16 (66.6%)	32 (34.0%)
Fate unknown	6 (9.7%)	.....	.....	6 (6.4%)
Total	63 (100 %)	7 (100 %)	24 (100 %)	94 (100 %)

no change and 2 (40.0 per cent) died, whereas of the 7 patients belonging to group 3, 2 (28.5 per cent) improved and 5 (71.5 per cent) died. In summary, of our 23 patients, on whom 26 operations were performed, 9 died, the case mortality being 39.1 per cent and the operative mortality 34.6 per cent. Seven patients died suddenly of acute respiratory failure, while for 2 others the cause of death was postoperative meningitis.

The operative results obtained in cases in which the cysticerci produce the clinical syndrome of an intracranial tumor are, therefore, encouraging. In 63.4 per cent of the cases reported in the literature, operative procedures yielded recovery or improvement; whereas in our own series recovery or improvement was noted in 72.6 per cent (table 4). Operative mortality in our cases was 16.6 per cent, and in the cases reported by others it was 17.8 per cent.

Group 1: Cysticercosis with Clinical

No.	Reference	Age, Yr.; Sex	Duration of Illness	Symptoms: Increased Intracranial Pressure	Symptoms: Focal Symptoms	Symptoms: Mental Changes
1	Vereo,[29] 1869	11 M	7 mo.	Headaches; bilateral choked disk	Epileptic seizures, starting in left hand; paresis of lower part of left facial nerve and of left hand	Soporific state
2	Maydl,[38] 1899	23 M	4 yr.	.....	Epileptic seizures, starting in fingers of left hand	.....
	Fischer, O., cited by Oppenheim [13]			.....	Epileptic seizures, starting in right foot	.....
3	Maragliano,[36] 1904 Krause,[12] 1911	31 M	4 mo.	Headaches; vomiting; bilateral choked disk	Paresis of lower part of left facial nerve; paralysis of left hand	Almost unconscious several hours before operation
4	Broca, A., and Waquet: Bull. et mém. Soc. de chir. de Paris **31**: 1119, 1905	? M	5 yr.	.....	Jacksonian seizures	.....
5	Pfeifer,[19] 1907	? ?	7 mo.	Headaches; bilateral choked disk	Paresis of lower part of facial nerve and of right hand	.....
6	Krause,[12] 1911	28 M	1 yr.	Headaches; dimness of vision; bilateral choked disk	Nystagmus on looking to the left	.....
7	Gabrielides: Ann. d'ocul. **19**: 265, 1916	17 F	5 mo.	Headaches; vomiting; dimness of vision; bilateral choked disk (8 D.)	Epileptic seizures in left extremities and staggering gait	.....
8	Lhermitte, J.; de Martel, T., and Nicolas: Rev. neurol. **1**: 364, 1924	25 F	1 yr.	.....	Right jacksonian seizures; paralysis of right hand	.....
9	Alurralde, M., and Sepich, M. J.: Rev. argent. de neurol. y psiquiat. **3**: 65, 1925; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **34**: 75, 1926	.. ..	.....	Headaches; vomiting; dimness of vision; bilateral choked disk	.....	.....
10	Bourquet and Merat [20]	29 F	10 yr.	Headaches; vomiting	Epileptic seizures in left extremities; paresis of lower part of right facial nerve	Melancholy
11	Himmelmann, W.: Deutsche Ztschr f. Chir. **205**: 362, 1927	18 F	.....	Headaches; vomiting; bilateral choked disk	Paresis of lower part of right facial nerve	.....
12	Pronin, A.: Sibir. arch. teoretic. i klic. med. **2**: 756, 1927; abstracted Zentralbl. f. d. ges. Neurol. u. Psychiat. **53**: 66, 1929	12 M	1 yr.	Headaches	Epileptic seizures in left extremities; paresis of left hand	.....
13	Rasdolsky,[42] 1927	25 M	4 yr.	Headaches; vomiting; Headaches	Epileptic seizures in left extremities; paresis of right side; sensory aphasia Epileptic seizures in left extremities; sensory aphasia	....
14	Arce, J.; Dimitri, V., and Balado, M.: A propósito de un caso de cisticercosis cerebral: operación; curación, Bol. Inst. de clin. quir. **4**: 371, 1928; abstracted Zentralbl. f. d. ges. Neurol. u. Psychiat. **53**: 66, 1929	.. M	.....	.....	Jacksonian seizures in left hand	.....
15	Mintz,[17] 1928	..	.....	Headaches; vomiting; bilateral choked disk	Epileptic seizures in left extremities	.....
16	Mintz,[17] 1928	..	.....	Headaches; vomiting; bilateral choked disk	Nystagmus on looking to either side; staggering gait	.....
17	Mintz,[17] 1928	..	.....	Headaches; vomiting; bilateral choked disk	Staggering gait	.....
18	Schmitz,[24] 1928	9 F	.....	Headaches; vomiting; bilateral choked disk	Paresis of both abducens nerves	.....
19	Weinberg, S. B.: Centralbl. f. allg. Path. u. path. Anat. **44**: 33, 1928	42 M	.....	Headaches; vomiting; dimness of vision; bilateral choked disk	Left hemiparesis	.....
20	Arce, J.; Balado, M., and Franke, E.: Arch. argent. de neurol. **4**: 7, 1929; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **54**: 529, 1930	15 M	.....	Headaches; vomiting; bilateral choked disk	Epileptic seizures in left extremities	.....

Symptoms of Cerebral Tumor: Additional Examinations				Preoperative Diagnosis	Operation	Results	Comment
Roentgenography	Blood	Cerebrospinal Fluid	Ventriculography				
Hyperostosis of right temporal bone	.....	.....	.....	Cysticercosis of brain	Right frontotemporal osteoplastic craniotomy; excision of single cysticercus	Death 4 days after operation	Autopsy: meningitis
.....	.....	.....	.....	Epilepsy; cysticercosis of brain	(1) Right frontotemporal osteoplastic craniotomy; excision of single cysticercus	Patient felt quite well 3 yr. after operation	
.....	.....	.....	.....	Cysticercosis of brain	(2) Excision of a single cysticercus from right motor region	Improvement	
.....	.....	.....	.....	Tumor of brain	Excision of 2 cysticerci from right motor region	Death 4 wk. after operation	Autopsy: several cysticerci on base of brain
.....	.....	.....	.....	Tumor of brain	Excision of single cysticercus from motor region	Recovery	
.....	.....	.....	.....	Cysticercosis of brain	Left frontotemporal osteoplastic craniotomy; excision of several cysticerci	No improvement	Diagnosis possible after puncture of brain
.....	.....	.....	.....	Tumor of brain?	Decompression of posterior fossa	Sudden respiratory failure second day after operation	Autopsy: several cysticerci on base of brain
.....	.....	.....	.....	Tumor of brain	Excision of several cysticerci from right frontal region	Improvement	
.....	.....	.....	.....	Tumor of brain	Excision of single cysticercus from left frontal region	Recovery	
.....	.....	.....	.....	Tumor of brain	Excision of single cysticercus from right temporal region	Improvement	
.....	.....	.....	.....	Cysticercosis of brain	Excision of single cysticercus	Improvement	Cysticercus on right arm
.....	.....	.....	.....	Tumor of brain	Excision of single cysticercus from left motor region	Distinct improvement	
.....	.....	.....	.....	Epilepsy	Excision of single cysticercus from right motor region	No improvement	
Distinct impressiones digitatae	.....	.....	.....	Tumor of brain	Excision of single cysticercus from left frontal region	Improvement	
				Cysticercosis of brain	Roentgen therapy	.....	
.....	.....	.....	.....	Tumor of brain	Excision of single cysticercus from right frontal region	Recovery	
.....	.....	.....	.....	Tuberculoma of brain	Excision of several cysticerci from right frontal region	Recovery	
.....	.....	.....	.....	Cysticercosis of brain	Removal of single cysticercus from fourth ventricle	Death 5 days after operation	
.....	.....	.....	.....	Tumor of brain	Removal of single cysticercus from fourth ventricle	Meningitis; death	
.....	.....	.....	.....	Tumor of brain	Excision of several cysticerci	Improvement	
.....	.....	.....	.....	Tumor of brain	Excision of cysticercus racemosus from right frontal region	Inflammation of the lungs; death	Autopsy: cysticercosis of brain
			Normal ventriculography	Tumor of brain	Excision of single cysticercus from right frontal region	Improvement	

No.	Reference	Age, Yr.; Sex	Duration of Illness	Symptoms: Increased Intracranial Pressure	Symptoms: Focal Symptoms	Symptoms: Mental Changes
21	Sejnson,[26] 1929	20 F	14 mo.	Headaches; vomiting; dimness of vision	Epileptic seizures in right extremities	.....
				.....	Epileptic seizures in left extremities	.....
22	Lejcinger, N.: Vestnik. khir. **62-63**: 187, 1930; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **61**: 800, 1931	.. ..	.....	Headaches; vomiting	Epileptic seizures in right extremities	.....
23	Christophe, D.; Divry, P., and Moreau: J. de chir. et ann. Soc. belge de chir. **9**: 324, 1932; abstracted, Zentralbl. f. d. ges, Neurol. u. Psychiat. **67**: 444, 1933	23 F	2 yr.	Headaches	Epileptic seizures starting in right hand; paresis of right hand	.....
24	Egas Moniz; Zoff, R., and Pacheco, L.: Encéphale **27**: 42, 1932	24 F	3 yr.	Headaches; vomiting; bilateral choked disk	Epileptic seizures, starting in left hand	.....
25	Schmite and Lemoyne: Cysticercose cérébrale de la régione pe'ia bulbare, Rev. neurol. **2**: 538, 1932	35 F	10 yr.	Headaches; vomiting; bilateral choked disk; dimness of vision	Paralysis of right side of body	.....
26	Allen, S., and Lowell, H.: **Ann. Surg. 97**: 1, 1933	.. ..	.....	Headaches; vomiting; bilateral choked disk	Left hemiparesis	.....
27	Horak, J., and Jedlicka, V.: Casop. lék. cesk., 1933, p. 1141; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **71**: 592, 1934	36 M	.....	Headaches	Epileptic seizures in right hand; right hemiparesis	.....
28	Behrman, S.: Proc. Roy. Soc. Med. **27**: 668, 1934	.. ..	6 yr.	Headaches; vomiting	Epileptic seizures in right extremities	.....
29	Denny-Brown, D.: Proc. Roy. Soc. Med. **27**: 667, 1934	31 M	7 yr.	Headaches; dimness of vision; bilateral secondary optic nerve atrophy	Epileptic seizures, starting in right extremities	.....
30	Hailes, W. A.: Australian & New Zealand J. Surg. **5**: 212, 1936	44 F	.....	Headaches; vomiting; dimness of vision; bilateral choked disk	Right hemiparesis; motor aphasia	.....
				Headaches; bilateral choked disk	Right hemiparesis	.....
31	Alajouanine, T.; Thurel, R., and Hornet, T.: Presse méd. **2**: 918, 1937	25 F	2 yr.	Headaches; secondary optic nerve atrophy; dimness of vision	Staggering gait; Romberg's sign swaying to left	.....
32	Adelstein, L. J.: J. Nerv. & Ment. Dis. **92**: 623, 1940	.. ..	.....	Headaches; vomiting; bilateral choked disk	Nystagmus on looking to each side; staggering gait	.....
33	Ray, B. S.: Arch. Neurol. & Psychiat. **45**: 494 (March) 1941	40 M	1 yr.	.....	Epileptic seizures in left extremities; left paralysis	.....
34	Arana and Asenjo,[23] 1945	33 M	2 yr.	Headaches; vomiting; bilateral choked disk	Staggering gait; diabetic disorders	.....
35	Arana and Asenjo,[23] 1945	25 F	4 mo.	Headaches; vomiting; bilateral choked disk	Singultus; vertigo	.....
36	Arana and Asenjo,[23] 1945	30 F	2 yr.	Headaches; vomiting; bilateral choked disk	Anosmia; staggering gait	.....
37	Ritchie, French and Titrud,[23] 1945	31 M	14 mo.	Headaches; dimness of vision; bilateral choked disk (20D.)	Slight paresis of right sixth cranial nerve	.....
38	Foerster, O., cited by Oppenheim [13]	.. ..	.....	.....	.....	.....
39	Hildebrand, cited by Oppenheim [13]	.. ..	.....	.....	.....	.....
40	Krause,[12] cited by Oppenheim, H.[13]	.. ..	.....	.....	.....	.....
41	Mikulicz and Tietzen, cited by Oppenheim [13]	.. ..	.....	.....	.....	.....
42	Poggio, cited by Oppenheim [13]	.. ..	.....	.....	Epileptic seizures	.....
43	Borchardt,[29] 1924	.. ..	.....	.....	.....	.....
44	Bucci, cited by Henneberg [8]	.. ..	.....	.....	.....	.....

Surgically Which Have Been Reported in the Literature—Continued

Additional Examinations							
Roentgenography	Blood	Cerebrospinal Fluid	Ventriculography	Preoperative Diagnosis	Operation	Results	Comment
.....	.....	.....	.....	Tumor of brain	(1) Excision of single cysticercus from right frontal region	8 wk. after operation—patient felt quite well	
.....	.....	.....	.....	Cysticercosis of brain	(2) Excision of two cysticerci from right frontal region	Improvement	
.....	.....	.....	.....	Tumor of brain	Excision of single cysticercus from left frontal region	Improvement	
.....	.....	.....	Ventricular system pushed to right	Tumor of brain	Excision of single cysticercus from left frontal region	Recovery	
.....	.....	.....	.....	Tumor of brain	Excision of single cysticerci from right frontal region	Improvement	
.....	Eosinophilic leukocytosis (5%)	Pleocytosis (96/cu. mm.)	Normal ventriculography	Tumor—cysticercosis?	(1) Decompression in left temporal region (2) Removal of three cysticerci from fourth ventricle	Death 6 wk. after operation (meningitis)	
.....	.....	.....	.....	Tumor of brain	Excision of cysticerci from right frontoparietal region	Improvement	
Distinct impressiones digitatae	.....	.....	.....	Tumor of brain	Excision of single cysticercus from left frontal region	Recovery	
Several small calcifications	.....	.....	.....	Cysticercosis of brain	Excision of cysticerci from left frontal region	Improvement	
Several calcifications	.....	.....	.....	Cysticercosis of brain	Decompression in right temporal region	Improvement	
.....	.....	.....	.....	Tumor of brain	(1) Excision of single cysticercus from left temporal region	3 wk. after operation patient felt well	
.....	.....	.....	.....	.....	(2) Excision of single cysticercus from same region	Recovery	
.....	.....	.....	Great dilatation of ventricular system	Tumor of cerebellum	Removal of single cysticercus from fourth ventricle	Death 7 days after operation	Autopsy: meningitis
.....	.....	.....	Dilatation of ventricular system	Tumor of cerebellum	Removal of single cysticercus from fourth ventricle	Improvement	
.....	.....	.....	.....	Tumor of brain	Excision of single cysticercus from right frontal region	Recovery	
.....	.....	.....	Great dilatation of ventricular system	.....	Removal of single cysticercus from fourth ventricle	Recovery	
.....	.....	.....	.....	.....	Removal of single cysticercus from fourth ventricle	Death 24 hr. after operation	
.....	.....	.....	Dilatation of ventricular system	.....	Removal of single cysticercus from fourth ventricle	Improvement	
.....	.....	.....	Anterior horn of right ventricle lifted; third ventricle pressed back	Tumor in parasellar region	Right frontal craniotomy; excision of single cysticercus from region of right optic nerve	Recovery	
.....	.....	.....	.....	Tumor of brain	Excision of single cysticercus from operculum	Improvement	
.....	.....	.....	.....	Tumor of cerebellum	Excision of single cysticercus from cerebellum	Death because of second cysticercus in fourth ventricle	
.....	.....	.....	.....	Tumor of brain	Excision of several cysticerci from frontal region	Improvement	
.....	.....	.....	.....	Tumor of brain	Excision of single cysticercus from frontal region	No improvement	
.....	.....	.....	.....	Cysticercosis of brain	Excision of two cysticerci	Improvement	
.....	.....	.....	.....	Tumor of brain	Excision of cysticerci from cortex	Recovery	
.....	.....	.....	.....	.....	Excision of several cysticerci from cortex	.....	

TABLE 5.—*Clinical Data on 71 Cases of Cysticercosis of the Brain Treated*

No.	Reference	Age, Yr.; Sex	Duration of Illness	Symptoms: Increased Intracranial Pressure	Symptoms: Focal Symptoms	Symptoms: Mental Changes
45	Cassirer, cited by Henneberg [3]	.. ..	.....	.....	.....	.....
46	Donath, cited by Henneberg [3]	.. ..	.....	.....	.....	.....
47	Gohl and Jacobi, cited by Henneberg [3]	.. ..	.....	.....	.....	.....
48	Goldstein, cited by Henneberg [3]	.. ..	.....	.....	.....	.....
49	Guecione, cited by Henneberg [3]	.. ..	.....	.....	.....	.....
50	Hoff (1931), cited by Henneberg [3]	.. ..	.....	.....	.....	.....
51	Walker and Hall, cited by Henneberg [3]	.. ..	.....	.....	.....	.....
52	Winkler, cited by Henneberg [3]	.. ..	.....	.....	.....	.....
						Group 2: Cysticercosis
53	Meyer, E.: J. f. Psychol. u. Neurol. **37**: 195, 1928	45 F	3 yr.	Headaches; vomiting; dimness of vision; bilateral choked disk	.....	.....
54	Verebely, T.: Orvosi hetil., 1936, p. 1035; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **84**: 521, 1937	.. ..	.....	Headaches; vomiting; dimness of vision; bilateral choked disk	Nystagmus on looking to either side; staggering gait	.....
						Group 3: Cysticercosis
55	Dandy [40]	41 M	7 mo.	Headaches; vomiting; dimness of vision, bilateral choked disk	Deafness; staggering gait	.....
56	Dandy [40]	28 F	1 yr.	Headaches; vomiting; dimness of vision; bilateral choked disk	Paresis of both abducens nerves; staggering gait; diabetic disorders	.....
57	Arana and Asenjo,[23] 1945	37 F	2 yr.	Headaches; vomiting; dimness of vision	Tinnitus	.....
58	Arana and Asenjo,[23] 1945	41 M	1 yr.	Headaches; vomiting; bilateral choked disk	Epileptic seizures; tinnitus	.....
59	Arana and Asenjo,[23] 1945	45 F	5 yr.	Headaches; vomiting; secondary optic nerve atrophy	.....	.....
60	Arana and Asenjo,[23] 1945	32	2 yr.	Headaches; vomiting; bilateral choked disk	Tinnitus; staggering gait	.....
61	Arana and Asenjo,[23] 1945	40 M	2 yr.	Headaches; vomiting; bilateral choked disk	Tinnitus; staggering gait	.....
62	Arana and Asenjo,[23] 1945	42 F	10 yr.	Bilateral choked disk	Tinnitus; diplopia; staggering gait	.....
63	Arana and Asenjo,[23] 1945	39 M	2 yr.	Headaches; vomiting	Diplopia; tinnitus; staggering gait	.....
64	Arana and Asenjo,[23] 1945	34 M	2 yr.	Headaches; vomiting; secondary optic nerve atrophy	Tinnitus	.....
65	Arana and Asenjo,[23] 1945	33 M	5 yr.	Headaches; vomiting; secondary optic nerve atrophy	Left hemiparesis; staggering gait	.....
66	Arana and Asenjo,[23] 1945	46 F	2 yr.	Headaches; vomiting; bilateral choked disk	Deafness and tinnitus of right ear	Euphoria
67	Arana and Asenjo,[23] 1945	38 F	4 yr.	Headaches; vomiting; bilateral choked disk	Epileptic seizures; left hemiparesis	.....
68	Arana and Asenjo,[23] 1945	34 M	6 mo.	Headaches; vomiting; bilateral choked disk	Left hemiparesis	.....
69	Arana and Asenjo,[23] 1945	46 F	2 yr.	Headaches; vomiting; bilateral choked disk	Diplopia	.....
70	Arana and Asenjo,[23] 1945	24 M	1 mo.	Headaches; vomiting	.....	.....
71	Winkel, cited by Henneberg [3]	.. ..	.....	.....	.....	.....

Additional Examinations							
Roentgenography	Blood	Cerebrospinal Fluid	Ventriculography	Preoperative Diagnosis	Operation	Results	Comment
.....	.....	.....	.....	.....	Excision of single cysticercus from cortex	Recovery	
.....	.....	.....	.....	.....	Excision of cysticerci from cortex	.....	
.....	.....	.....	.....	.....	Excision of cysticerci from cortex	.....	
.....	.....	.....	.....	.....	Excision of single cysticercus from cortex	Recovery	
.....	.....	.....	.....	.....	Excision of cysticerci from cortex	.....	
.....	.....	.....	.....	.....	Removal of single cysticercus from fourth ventricle	Improvement	
.....	.....	.....	.....	.....	Excision of cysticerci from cortex	.....	
.....	.....	.....	.....	.....	Excision of cysticerci from cortex	.....	
Producing Cerebral Edema							
.....	.....	.....	.....	Tumor of brain	Left frontoparietal osteoplastic craniotomy; decompression	No improvement; death after 11 yr.	Autopsy: cysticercosis of base of brain
.....	.....	.....	.....	Tumor of cerebellum	Decompression of posterior cranial fossa	Meningitis: death	Autopsy: cysticercosis of brain
Producing Hydrocephalus Internus							
.....	.....	Pleocytosis (80/cu. mm.)	Great and symmetric dilatation of ventricular system	Tumor of brain	Decompression of posterior cranial fossa	Death	Autopsy: cysticercosis of base of brain
.....	.....	.....	Symmetric dilatation of ventricular system	Tumor of brain	Right frontal craniotomy	Death	Autopsy: racemose cysticercosis
.....	.....	.....	Dilatation of ventricular system	.....	Decompression of posterior cranial fossa; disclosure of racemose cysticercosis	Discharged after 4 wk.	Death after 2 mo. at home
.....	.....	.....	Dilatation of ventricular system	.....	Decompression of posterior cranial fossa; disclosure of racemose cysticercosis	Death after 7 wk.	Autopsy: racemose cysticercosis
.....	.....	.....	Dilatation of ventricular system	.....	Decompression of posterior cranial fossa; disclosure of racemose cysticercosis	Discharged after 4 wk.	
.....	.....	.....	Dilatation of ventricular system	.....	Decompression of posterior cranial fossa; disclosure of racemose cysticercosis	Death after 4 wk.	Autopsy: racemose cysticercosis
.....	.....	.....	Dilatation of ventricular system	.....	Decompression of posterior cranial fossa; disclosure of racemose cysticercosis	Death after 4 wk.	Autopsy: racemose cysticercosis
.....	.....	.....	Dilatation of lateral ventricles	.....	Decompression of posterior cranial fossa; disclosure of racemose cysticercosis	Discharged after 5 days	
.....	.....	.....	Dilatation of ventricular system	.....	Decompression of posterior cranial fossa	Death after 4 days	Autopsy: racemose cysticercosis
.....	.....	.....	Dilatation of ventricular system	.....	Decompression of posterior cranial fossa; disclosure of racemose cysticercosis	Discharged after 5 wk.	
.....	.....	.....	Dilatation of ventricular system	.....	Decompression of posterior cranial fossa; disclosure of racemose cysticercosis	Death after 7 days	Autopsy: racemose cysticercosis
.....	.....	.....	Dilatation of ventricular system	.....	Decompression of posterior cranial fossa; disclosure of racemose cysticercosis	Discharged after 10 days	
.....	.....	.....	Dilatation of ventricular system	.....	Decompression of posterior cranial fossa; disclosure of racemose cysticercosis	Improvement	
.....	.....	.....	Dilatation of ventricular system	.....	Decompression of posterior cranial fossa; disclosure of racemose cysticercosis	Death after some hours	Autopsy: racemose cysticercosis
.....	.....	.....	Dilatation of ventricular system	.....	Removal of single cysticercus from fourth ventricle	Death after 3 days	
.....	.....	.....	Dilatation of ventricular system	.....	Removal of single cysticercus from fourth ventricle	Recovery	
.....	.....	.....	.....	.....	Decompression of posterior cranial fossa; disclosure of racemose cysticercosis	Death	

TABLE 6.—*Clinical Data on 23 Cases of Cysticercosis*

Group 1: Cysticercosis with the

No.	Initials and Date of Admission	Age, Yr.	Sex	Duration of Illness	Symptoms		
					Increased Intercranial Pressure	Focal Symptoms	Mental Changes
1	O. K., 29/11/37	25	F	6 mo.	Headaches; vomiting; dimness of vision; bilateral choked disk	Epileptic seizures, starting in left side of face; paresis of lower part of left facial nerve; dilatation of right pupil; left hemiparesis	.....
2	M. K., 1/8/38	37	F	2 yr.	Headaches; vomiting; dimness of vision; bilateral secondary atrophy of optic nerve	Paresis of right sixth, seventh and twelfth cranial nerves; staggering gait; Romberg sign to back	.....
3	A. W., 15/10/38	34	M	6 mo.	Headaches; vomiting; dimness of vision; bilateral choked disk; pulse, 56	Dilatation of left pupil; paresis of left fifth, seventh and eighth cranial nerves; nystagmus on looking to either side; staggering gait	.....
4	M. P., 22/3/39	38	F	5 yr.	Headaches; vomiting; pulse, 60	Bilateral primary optic atrophy; hemianopsia binasalis	Visual and auditory hallucinations
5	H. K., 5/4/40	41	F	16 mo.	Headaches; vomiting; bilateral choked disk	Attacks of burning sensations in face and upper extremities, accompanied with hyperhydrosis of hands; lower extremities covered with "gooseflesh"	.....
6	W. F., 16/12/41	40	F	7 mo.	Headaches; vomiting; bilateral choked disk	Dilatation of left pupil; slight left hemiparesis	.....
7	J. S., 7/4/43	32	M	6 mo.	Headaches; vomiting; bilateral choked disk; pulse, 54	Jacksonian seizures in left side of face and in left hand; paresis of lower part of left facial nerve	Loss of orientation for time, place and current events
8	J. G., 14/5/43	35	F	3 yr.	Headaches; vomiting; bilateral choked disk (3-4 D.)	Nystagmus on looking to left; staggering gait; Romberg sign to left	.....
9	G. S., 1/9/43	26	F	2 yr.	Headaches; vomiting; dimness of vision; bilateral choked disk	Staggering gait; Romberg sign to right	.....
10	E. S., 5/11/45	27	M	7 mo.	Headaches; bilateral choked disk (2.5-3.0 D.)	Jacksonian seizures in left hand; dilatation of right pupil; paresis of lower part of left facial nerve; slight left hemiparesis	.....
11	W. P., 2/8/45 and 7/11/45	31	F	2 yr.	Headaches; vomiting; bilateral choked disk (3.0-3.5 D.)	Epileptic seizures in left side of body with loss of consciousness; numbness of right side of body on 3 occasions; dilatation of left pupil	.....
					Headaches; secondary optic nerve atrophy	Epileptic seizures in right hand; loss of consciousness; slight paresis of right hand; dilatation of left pupil	.....

Clinical Symptoms of Cerebral Tumor

Additional Examinations							
Roentgenologic	Blood	Cerebrospinal Fluid	Ventriculography	Preoperative Diagnosis	Operation	Results	Comment
.....	.....	.....	.....	Tumor in right frontal region	Right frontoparietal osteoplastic craniotomy; excision of a single cysticercus from operculum	Patient discharged 3 wk. after operation; no symptoms 2 yr. later	
Sella turcica almost entirely decalcified	Eosinophilic leukocytosis, (2%)	.....	.....	Tumor of posterior fossa	Decompression of posterior cranial fossa; removal of 2 cysticerci from fourth ventricle; disclosure of 2 cysticerci in region of right facial nerve	Distinct improvement	
.....	.....	.....	.....	Tumor of left eighth cranial nerve	Decompression of posterior cranial fossa; removal of single cysticercus from region of left eighth cranial nerve	Improvement	
Destruction of dorsum sellae	.....	.....	.....	Tumor in region of optic chiasm	Right frontal craniotomy; removal of single cysticercus from optic chiasm	Patient discharged 2 wk. after operation with distinct improvement	21/3/46: patient felt quite well
Destruction of dorsum sellae	Eosinophilic leukocytosis, (4%)	.....	Hydrocephalus of both lateral and third ventricles; no air in aqueduct or fourth ventricle; small areas of calcification in third ventricle	Cysticercus or tuberculoma of third ventricle	Right frontal osteoplastic craniotomy; removal of 6 cysticerci from region of optic chiasm	Patient discharged 2 wk. after operation, entirely free of symptoms	
Clinoid processes decalcified	White cells 10,000	Protein 1.5 %	Symmetric dilatation of ventricular system	Tumor of third ventricle	Right frontal craniotomy; Stookey operation	Death 24 hr. after operation (sudden respiratory failure)	Autopsy: 3 cysticerci in lateral ventricle
.....	White cells 12,200	.....	.....	Tumor in right frontal region	Right frontotemporal osteoplastic craniotomy; removal of 30 cysticerci from frontal and temporal region	Improvement	
Distinct impressiones digitatae	.....	.....	.....	Tumor of posterior cranial fossa	Decompression of posterior cranial fossa; removal of single cysticercus from fourth ventricle	Patient discharged 2 wk. after operation, free of symptoms	1/3/46: patient felt fairly well
Distinct impressiones digitatae	.....	.....	Great and symmetric dilatation of lateral ventricles; third ventricle filled with air in anterior part	Tumor of third ventricle	Right frontal craniotomy; revision of third ventricle; Stookey operation	Death 36 hr. after operation (sudden respiratory failure)	Autopsy: single cysticercus in fourth ventricle
.....	Eosinophilic leukocytosis (2%)	Protein 0.99 %; pleocytosis (42/cu. mm.)	.....	Tumor in right frontal region	Right frontal osteoplastic craniotomy; removal of 3 cysticerci from frontal region	Patient discharged 17 days after operation, entirely free of symptoms	6 mo. after operation patient felt quite well
.....	Eosinophilic leukocytosis (2%)	.....	.....	Cysticercosis of the brain(?)	Right frontotemporal osteoplastic craniotomy; removal of 7 cysticerci from cortex	Patient discharged 17 days after operation, free of symptoms; 7 wk. later patient returned to department	
.....	.....	.....	.....	Cysticercosis of brain	Left frontotemporal osteoplastic craniotomy; excision of 3 cysticerci from frontal region	Patient discharged 4 wk. after operation, with improvement	

TABLE 6.—*Clinical Data on 23 Cases of Cysticercosis Treated*

Group 2: Cysticercosis

No.	Initials and Date of Admission	Age, Yr.	Sex	Duration of Illness	Symptoms		
					Increased Intercranial Pressure	Local Symptoms	Mental Changes
12	L. S., 24/11/42	35	F	4 mo.	Headaches; vomiting; bilateral choked disk (2.0-2.5 D.)	Paresis of left abducens and facial nerves; paresis of left hand; staggering gait	Loss of orientation for time, place and current events
13	J. G., 30/11/42	28	F	5 mo.	Headaches; bilateral choked disk (2.5 D.)	Epileptic seizures with loss of consciousness	.....
14	R. S., 4/8/45	13	M	8 mo.	Headaches; vomiting; bilateral choked disk; blindness	Dilatation of right pupil; paresis of lower part of left facial nerve	Loss of orientation for time, place and current events; very great excitement; visual and auditory hallucinations
15	K. M., 24/:/46	10	F	4 mo.	Headaches; vomiting; dimness of vision; secondary optic nerve atrophy	Slight nystagmus on looking to right	Great excitement; visual hallucinations
16	K. M., 23/3/46	42	F	8 mo.	Headaches; vomiting; bilateral choked disk (1.5 D.)	.....	Loss of orientation for time, place and current events
							Group 3: Cysticercosis
17	J. R., 3/12/35	57	F	2 yr.	Headaches; vomiting; bilateral choked disk (6.0-10.0 D.)	Staggering gait; Romberg sign to back	.....
18	B. W., 22/2/36	31	F	5 yr.	Headaches; dimness of vision	Nystagmus on looking to either side; paresis of right fifth and seventh cranial nerves; Romberg sign to right	.....
19	T. K., 14/5/39	51	M	5 mo.	Headaches; dimness of vision; bilateral choked disk	Paresis of left facial nerve; deafness on right	Loss of orientation for time, place and current events
20	J. W., 16/12/39	46	M	18 mo.	Headaches; dimness of vision; bilateral choked disk	Dilatation of right pupil; paresis of lower part of left facial nerve	.....
21	K. R., 17/6/42	37	M	7 mo.	Headaches; bilateral choked disk	.....	.....
22	B. S., 25/8/43	39	M	4 mo.	Headaches; vomiting; bilateral choked disk (3.0-5.0 D.)	Paresis of lower part of right facial nerve; slight paresis of right hand; motor aphasia	.....
23	G. S., 21/1/46	50	F	3 mo.	Headache	Nystagmus on looking to either side	Loss of orientation for time, place and current events

Producing Cerebral Edema

Additional Examinations								
Roentgenologic	Blood	Cerebrospinal Fluid	Ventriculography	Preoperative Diagnosis	Operation	Results	Comment
.....	.....	Protein 0.75 %; pleocytosis 12/cu. mm.	Both lateral ventricles very narrow	Swelling of brain	(1) Decompression in right temporal region (2) Left frontotemporal osteoplastic craniotomy; excision of cysticerci from cortex	Excitement immediately after operation; patient left hospital 4 wk. later, without distinct improvement	
.....	.....	Protein 0.6 %; pleocytosis 95/cu. mm.	Both lateral and third ventricles narrow	Swelling of brain(?)	Decompression in left temporal region	15 hr. after operation, sudden respiratory failure and death	Autopsy: multiple cysticerci in brain
.....	White cells 8,500 eosinophilic leukocytosis (7%)	Protein 0.99 %; pleocytosis 19/cu. mm.	..... brain	Cysticercosis of brain	Right frontal osteoplastic craniotomy; distinct swelling of brain; excision of 5 cysticerci from cortex and 1 cysticercus from region of right optic nerve	Patient discharged 2 wk. after operation; mental changes disappeared; blindness	10/8/46: patient feels subjectively quite well, although blind
Distinct impressiones digitatae	White cells 9,200; eosinophilic leukocytosis (3%)	.....	Ventricle system very narrow	Cysticercosis of brain	(1) Right temporal decompression (2) Left temporal decompression	Death 3 mo. after operation	Autopsy: cysticercosis of brain; meningitis
.....	.....	.....	Ventricle system narrow, pushed to left	Cysticercosis of brain	Right frontotemporal osteoplastic craniotomy; excision of 14 cysticerci from cortex	Patient discharged 3 wk. after operation, with improvement	Patient infected with solium
Producing Hydrocephalus Internus							
Distinct impressiones digitatae	.....	.....	Great and symmetric dilatation of ventricular system	Obstruction of foramen of Luschka and Magendi	Decompression of posterior cranial fossa; removal of 1 cysticercus from fourth ventricle	Death 4 days after operation (meningitis)	Autopsy: 12 cycticerci in lateral and fourth ventricles
.....	.....	.....	Great and symmetric dilatation of ventricular system; aqueduct of sylvius and fourth ventricle not visible	Lesion of posterior cranial fossa	Decompression of posterior cranial fossa	Death 2 wk. after operation	Autopsy: cysticercosis of base of brain
.....	.....	.....	.....	Tumor in right frontal region(?)	Right frontal osteoplastic craniotomy; hydrocephalus internus; decompression	Death 24 hr. after operation (sudden respiratory failure)	Autopsy: cysticercosis of base of brain
.....	.....	Protein 0.6 %	.....	Tumor in right frontal region(?)	Right frontal osteoplastic craniotomy; hydrocephalus internus; decompression	Death 4 days after operation (sudden respiratory failure)	Autopsy: racemose cysticercosis of brain
.....	.....	.....	Dilatation of both lateral ventricles	Tumor of third ventricle	Right frontal osteoplastic craniotomy; excision of 1 cysticercus from cortex	Discharged 2 wk. after operation with improvement	
.....	.....	.....	Great and symmetric dilatation of ventricular system	Cysticercosis of brain	Right frontal osteoplastic craniotomy; excision of cysticerci from cisterna chiasmatis; Stookey operation	Discharged 4 wk. after operation with improvement	
Calcification in right temporooccipital region	.....	Protein 0.3 %; pleocytosis 6/cu. mm.	Dilatation of ventricular system	Cysticercosis of brain	Decompression of right temporal region	Death 30 hr. after operation (sudden respiratory failure)	Autopsy: 12 cysticerci disseminated on both hemispheres

We agree with Henneberg [3] that removal of a single parasitic cyst from the brain, the fourth ventricle or the cerebellopontile angle is not only less difficult than removal of another type of tumor but, on the contrary, represents a procedure which is much less damaging. It seems to us, therefore, that in every case in which a diagnosis of localized cerebral cysticercosis is made, operation should be performed. If the parasitic cysts are multiple and cannot all be removed, no great harm is done by removing those which are accessible, while extirpation of a single cysticercus may lead to complete and lasting recovery. In cases in which the cysticerci produce severe edema of the brain, the operative results are much poorer; yet in 2 of the 5 cases belonging to that group improvement was definite. It is worth while, therefore, to try operation even in such cases. When there is no improvement, roentgen therapy may be tried, Lowenthal (1911), Bourquet and Merat,[20] Rasdolsky [41] (1927), Morawiecka [22] and Tyczka [15] reporting good results. Henneberg [3] also recommended irradiation, in the belief that roentgen rays stop the inflammatory process in the meninges and in the brain that always accompanies cysticercosis. In 2 of our cases roentgen therapy was given as an adjunct to the operative treatment, without any effect, however, in either instance.

The most unfavorable results of operative treatment are to be expected in cases of cysticercosis producing hydrocephalus internus, the majority of parasites being located at the base of the brain. Indeed, of the 17 patients operated on by others, 11 died, whereas of our 7 patients, only 2 were improved and the rest died. In this group of cases the patient may be helped only by one of the palliative procedures, whether it be a simple subtemporal decompression, Stookey's operation or the Torkildsen procedure. The prognosis, of course, is in agreement with the data presented: In the cases of group 1, it is good for the most part; in the other two groups it is doubtful or definitely poor.

SUMMARY AND GENERAL CONCLUSIONS

1. An attempt is made to classify the cases of cerebral cysticercosis in three groups according to the pathologic and clinical pictures produced. Group 1 is composed of cases in which the cysticercus causes symptoms of an intracranial tumor, i.e., of intracranial hypertension and of focal significance. Group 2 includes cases in which the parasitic cyst produces chiefly edema of the brain, betraying itself by symptoms of intracranial hypertension and psychic disturbance. Rapid loss of vision characterizes this group, as well as group 3. Group 3 includes cases in which the cysticerci, located mainly at the base of the brain,

41. Rasdolsky, J.: Le cysticerque du cerveau: Operation, radiotherapie, resultat favorable, Rev. neurol., 1927, p. 530.

produce an internal hydrocephalus, with symptoms of intracranial hypertension and atypical and variable focal signs. Some psychic disturbances are seen also in this group; however, they are not so conspicuous as in group 2.

2. The purpose of classification of cysticercosis cerebri is facilitation of the choice of surgical procedure and the making of a prognosis.

3. Without a history of infection with T. solium; in the absence of demonstration of the parasites in the subcutaneous tissue, muscle or eye or other structures, and in the absence of eosinophilia of the blood and/or the cerebrospinal fluid, an accurate diagnosis is usually impossible. As a rule, the diagnosis is only a tentative one.

4. On the basis of a review of 94 cases of cerebral cysticercosis treated surgically, the following conclusions are drawn:

Contrary to current opinion, operative treatment is followed by good results in about 50 per cent of cases.

Cysticercosis cerebri, producing symptoms of intracranial tumor, should always be treated surgically. In our experience, operative treatment yielded recovery or improvement in 72.6 per cent of the cases.

The parasites, which are usually numerous and which produce cerebral swelling, can be only partially removed; yet even partial excision, accompanied with decompression of the brain, may result in improvement in the patient's condition.

Hydrocephalus internus, resulting from the presence of the usually multiple cysts, located in the basal cisternae, calls for a palliative procedure—short-circuiting the circulation of the cerebrospinal fluid.

APPENDIX

The clinical data on the 71 cases of cysticercosis of the brain treated surgically which have been reported in the literature and the 23 cases personally observed are presented in tables 5 and 6.

Neurological Clinic.

SCOLIOSIS AS A MANIFESTATION OF DISEASE OF THE CERVICOTHORACIC PORTION OF THE SPINAL CORD

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THE PRESENCE of scoliosis, or curvature of the spine, must always suggest the possibility of disease of the spinal cord, often correctable.

Traditionally, scoliosis, which is usually thought of as an orthopedic problem, is looked on as related to a disease of bone and muscle alone or to irreparable or unidentifiable disease which has afflicted the central nervous system, or as being idiopathic. It is generally recognized that a patient with disease of the spinal cord may have, among other things, scoliosis or that scoliosis may, in fact, be of such degree that it itself damages the cord. Not sufficiently prominent in the common consideration of clinicians, however, is the fact that scoliosis may be the earliest sign of disease of the spinal cord, or the first sufficiently recognized to bring the patient to the physician; that it may indicate the presence of a process which may be retarded, halted or cured. When one considers the limited recuperative powers of the spinal cord, the reason for emphasizing the possible significance of this sign is obvious. The thesis that scoliosis must of itself be regarded as an early sign of disease of the spinal cord is supported by a discussion of 10 cases in which the deformity was one of the earliest signs or was the principal presenting symptom.

REPORT OF CASES

CASE 1.—*Platybasia with congenital anomaly of the cervical portion of the spine and medullocerebellar traction displacement (Arnold-Chiari malformation).*

L. F., a boy aged 15 years, was admitted to the University of California Hospital in January 1943, with a history of "a crooked back" for six years and of "fainting spells" for two months.

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When the child was 9 years of age, his parents first noticed the development of a curvature of the spine, although evidence of the scoliosis was present in photographs taken at the age of 7. A diagnosis of poliomyelitis was made then, despite the absence of a history of any definite acute episode. For the following six years the patient was treated by various orthopedic procedures, without benefit. At the age of 11 years he had first noticed weakness of the left thumb followed by gradual extension of the weakness to the hand and arm. Three months before his admission weakness first appeared in the legs. During the two months preceding entrance to the hospital he had several attacks of weakness and syncope.

There was nothing significant in the past or the family history.

Except for a slight nystagmus in lateral gaze in either direction, function of the cranial nerves appeared normal. There was moderate atrophy of all the muscles of the left hand, forearm, arm and shoulder girdle. The biceps reflex was absent bilaterally, and the remaining deep reflexes were hyperactive on the left side. There were sustained ankle and patellar clonus on the left side, and the Babinski sign was elicited on that side. Sensory examination disclosed hypesthesia over the first to the eighth thoracic dermatomes. There was prominent thoracic scoliosis, with convexity to the left, the curvature being accentuated on standing.

Studies of the cerebrospinal fluid showed normal pressure, cell count and chemical constituents; there was no evidence of spinal subarachnoid block. Roentgenologic examination showed a thoracic rotary scoliosis with the apex at the eleventh thoracic vertebra; roentgenograms of the skull disclosed platybasia, with fusion of the right lateral mass of the first cervical vertebra to the occiput and with a corresponding defect of the arch.

Operation confirmed the presence of the bony changes shown in the roentgenogram. The dura was remarkably thickened throughout the occipital and upper cervical region; the meninges were adherent to each other as well as to the cord and cerebellum. The cerebellar tonsils projected well into the spinal canal, the protrusion being greater on the right than on the left, and compressed the cervical portion of the cord and the medulla, to which they were intimately attached. These adhesions were interrupted, and the involved structures were decompressed.

Since this decompression the weakness has gradually improved, and no further fainting attacks have occurred. Orthopedic measures have been instituted to correct the scoliosis.

All our patients with platybasia have had some degree of scoliosis; in this case the curvature was regarded as the primary sign. Involvement of the spinal cord in the anomalous complex, most obvious in the bone, usually has appeared later or, as is shown later, has been associated with intrinsic disease of the spinal cord, notably syringomyelia. The role of the medullocerebellar traction displacement is important here, for it contributes in large degree, we believe, to the actual advance of the disease process.

CASE 2.—*Platybasia; Klippel-Feil syndrome; cervical hydromyelia; hemangioma of the cisterna magna; neurofibromatosis (von Recklinghausen's disease), and cervical meningeal adhesions.*

J. N., a white man aged 32, was admitted to the University of California Hospital in February 1946, with the complaint of progressive curvature of the spine with weakness and stiffness of the right arm and leg.

At the age of 16 years he had an acute febrile illness, during which both the patient and his parents noticed the curvature of his spine for the first time. Within a few days after this there appeared stiffness and weakness in his right shoulder, arm, forearm and hand; slight unsteadiness on his feet, and intermittent diplopia. All these signs except the scoliosis disappeared completely in a few

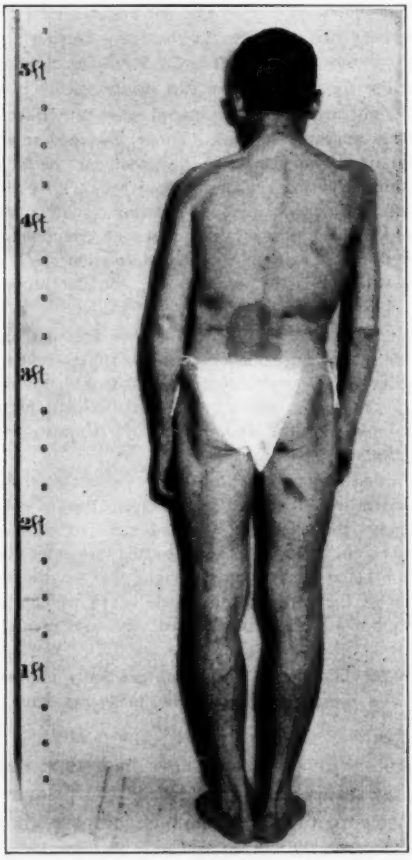

Fig. 1 (case 2).—Scoliosis associated with platybasia, the Klippel-Feil syndrome, cervical hemangioma of the cisterna magna and neurofibromatosis (von Recklinghausen's disease). The scoliosis was the first sign of the disease of the spinal cord.

months. Ten months later he had another episode, similar to the first, which left him with weakness of grip and loss of dexterity in his right hand.

Four years after the original attack, the patient noticed occasional tightening and impaired coordination of the right leg. This was followed through the ensuing years by progression of the scoliosis and general loss of use of the right

side. Loss of sensation for pain and temperature on the left side of his body appeared two years before admission. No sphincter disturbances had been noted.

No relevant history of past personal or familial disease was given.

The patient was small of stature with numerous café au lait spots over the trunk and spine. There was a rotary cervicothoracic scoliosis (fig. 1), with the convexity to the right. Atrophy with fibrillation of the muscles of the shoulder girdle, arm, forearm and hand on the right was present. All the deep reflexes were hyperactive, and Babinski and Hoffmann signs were elicited on the right side. The abdominal reflexes were absent. There were loss of sensation for pain and temperature over the second to the fourth dermatomes bilaterally and a relative loss of pain and temperature sense over the entire left side of the body except the sacral segments.

The cerebrospinal fluid was normal. There was a partial spinal subarachnoid block, demonstrated by myelogram, at the foramen magnum. Roentgenographic examination showed platybasia and fusion of the second and third cervical vertebrae.

At operation the left side of the foramen magnum was observed to be fused with the left arch of the atlas. The laminas of the second and third cervical vertebrae were fused.

Dense adhesions involved the dura at the foramen magnum, the dura here being 3 to 4 mm. in thickness. A large angioma filled the cisterna magna. There was hydromyelia of the cervical portion of the cord from the third cervical segment to the medulla. This cavity was opened; the adhesions were interrupted, and the cord was decompressed. Removal of the angioma was not felt to be feasible.

The progression of the disease was halted for a period of two years after operation. The reappearance of symptoms then was treated by irradiation of the region of the angioma.

The hydromyelia and angioma were regarded as major factors in the disease process in this case, though, as shown in case 1, the role of platybasia could not be ignored. The whole pathologic complex is possibly part of the von Recklinghausen syndrome, though the scoliosis usually regarded as related to neurofibromatosis is due to change in the bone itself. The degree of incapacity present in this patient could certainly have been reduced or retarded had the clinical significance of the scoliosis been recognized earlier.

CASE 3.—*Congenital anomaly of the occipital and cervical vertebrae with cyst (possibly hydromyelia) of the cervical portion of the spinal cord.*

G. B., a white man aged 31, presented himself for study because of long-standing, progressive thoracic scoliosis and spastic paralysis.

The patient was said to have been a normally healthy child until the age of 3½ years, when he had what was diagnosed as measles. While he was convalescing, the parents noted for the first time a curvature of the thoracic portion of the spine. Clumsiness of the legs, which appeared at about the same time, was attributed to weakness from the acute illness. Treatment of the scoliosis was immediately instituted, and braces, casts and exercises were tried in succession, without benefit. The motor loss in the legs did not advance at first, but after the age of 7 years this, too, progressed and was treated chiefly by exercises.

By the age of 15 years the patient realized there was sensory impairment in the legs, and by the age of 21 motor control of the right arm was beginning to fail. Thereafter, the scolosis seemed stationary, but motor and sensory loss continued to increase slowly but steadily.

The striking abnormality seen on physical examination was a thoracolumbar scoliosis to the right and a cervicothoracic scoliosis to the left. The entire thoracic cage was rotated to the right, and the right scapula was prominent. The cranial nerves bore no evidence of related dysfunction. The muscles of the left arm seemed to be of normal power but were hypertonic. On the right they were weak and atrophied, particularly above the elbow. There was moderate spastic weakness of the legs, particularly on the right. Except for absence of the biceps reflex on the right the deep reflexes were hyperactive, with ankle clonus and plantar extensor response bilaterally. Sensation to pain and temperature was lost over the right half of the trunk, the right shoulder and arm and the left shoulder. Vibratory sense was diminished in the legs. Other modalities seemed intact.

Roentgenograms showed a congenital anomaly of the base of the skull and of the sixth and seventh cervical vertebrae on the right. An incomplete subarachnoid block was demonstrated at the sixth cervical level.

At operation, by Dr. Howard C. Naffziger, the entire cervical region of the cord was observed to be cystic, the wall being paper thin on the right side posteriorly. The cyst contained 40 to 50 cc. of fluid, under pressure. The cavity was opened widely, and the cord was left decompressed.

After the regression anticipated immediately after operation, as a result of the abrupt decompression, motor activity returned to the preoperative level and sensation improved, particularly appreciation of pain and temperature.

The signs of disease of the spinal cord were, of course, obvious when the described studies were carried out. The scoliosis noted at the age of 3½ years should then have raised the question of spinal disease, for further investigation. The appearance later of motor changes in the legs should certainly have settled the problem. By pursuit of these clues, the earlier identification of the underlying process would probably have been made, and the degree of irreparable damage to the cord would have been reduced.

CASE 4.—*Intramedullary cyst of the thoracic portion of the spinal cord.*

G. G., a white girl aged 14, was referred because of advancing scoliosis of eleven years' duration and progressive paraplegia in flexion with sensory changes over a period of four years.

The patient was said to have been normal until the age of 3 years, when she had an acute febrile illness diagnosed as "poliomyelitis of the shoulder girdles and trunk." Further details are unknown. At the age of 8 years she was studied because of the appearance of thoracic scoliosis and was treated by conservative measures, including a turnbuckle cast, until she was 10 years of age, when a spinal fusion was done in two stages. About the time of the second procedure a flexion contracture was noted first in the right leg and later in the left. In spite of traction and "Kenny packs," these advanced so that by the end of the year there was an estimated contracture of 40 degrees in the right knee and of 15 degrees in the left knee. During the next three years, braces and exercises

were employed, but, despite them, she finally lost the ability to walk without help.

When she was examined at the age of 14 years, there was good power in the shoulders and arms, but weakness of grip and atrophy of the intrinsic muscles of the hands were present. The legs, which were flexed at thigh and knee to approximately 45 degrees when the patient was at rest, could be extended fully with force. The reflexes were hyperactive in the legs, with ankle clonus and a Babinski response bilaterally. Sensory changes were not observed. The spinal fluid pressure was normal, but the protein content was 250 mg. per hundred cubic centimeters. There was no spinal subarachnoid block.

For a month, continuous traction was applied to the legs. At the end of this time all reflexes in the upper extremities had disappeared, though power remained as before. Hypalgesia was found below the first lumbar level on the left and below the third lumbar segment on the right. Vibratory and position senses in the legs were absent. By myelographic studies a complete block was demonstrated at the ninth thoracic vertebra.

At operation, by Dr. Howard Brown, an intramedullary cyst, which extended from the fifth to the ninth thoracic vertebra, was opened. The adjacent portion of the cord was firm. The entire area was decompressed. No biopsy was made.

After operation the corrective and supportive orthopedic measures were resumed.

This is another case of a slowly progressive cystic lesion which, in the absence of cytologic proof, may for our purpose be classified with syringomyelia and the cystic tumors. It is impossible to say how soon alteration in the cord itself could have been recognized by myelography or by surgical exposure. The delay, as in case 1, was due to a previous diagnosis—actually a guess—of poliomyelitis. The reported patency of the spinal subarachnoid channel only one month before a complete block was demonstrated suggests that the final progress of the disease of the cord was rapid. It is presently felt, however, that earlier studies might have produced evidence which could have been used to retard, if not halt, the progress of the patient's debility.

A review of the other cases of cystic lesions of the cervical and thoracic portions of the spinal cord seen at this university revealed that scoliosis has uniformly been noted. These cases are not included here, however, as other clinical signs were consistently more prominent, and in some cases the patient himself was unaware of the presence of the scoliosis. These observations, nonetheless, have further impressed us with the value of this clinical sign, particularly in the presence of the general pathologic state described.

CASE 5.—*Thoracic spina bifida with congenital anomaly of the adjacent part of the spinal cord.*

E. G., a white boy aged 13 years, was admitted because of a "crooked back" and progressive loss of use of the legs.

When the child was adopted, at the age of 5 weeks, the foster parents had noted "curvature of the spine," clubfoot on the right and facial asymmetry, said to

be due to a birth injury. The clubfoot was straightened within a few months, but the spinal curvature remained, though for a while it was thought to be improved. The child did not learn to walk well, and at the age of 2 years the parents were told that the entire disability in development, including the scoliosis, was related to spina bifida in the thoracic region. The disability of the legs was corrected by a series of operations, but the scoliosis and related spina bifida were disregarded, the parents being told that nothing more could be done.

After a few years the patient once more began to experience difficulty in walking, which became progressively worse. Increase in the spinal curvature was moderate. At the age of 13 years the patient was taken to the San

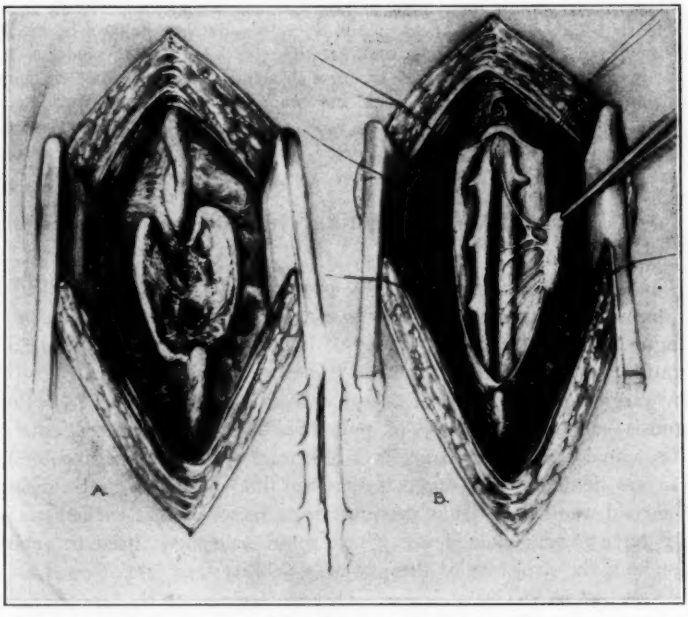

Fig. 2 (case 5).—Thoracic spina bifida and congenital failure of closure in the cord lying beneath. Note the anomaly of roots on the right side of the cord and the abortive area granulosa, which anchored the cord to the meninges.

Francisco Shriners Hospital for Crippled Children. There the possible role of the spina bifida in his complaints and response to treatment was considered and the possible presence of a reparable related lesion of the cord was recognized. The patient was referred to the University of California Hospital for further study of this aspect of the problem.

At the time of his admission there was noted a scoliokyphosis in the lower thoracic region, with convexity to the right. Somewhat above the convexity was a palpably bifid spine apparently involving the third to the fifth segments and covered with a hairy skin. The lower extremities, moderately weak, were spastic and were maintained in flexion. Some contractures were present. There was diminution of the senses of joint position and vibration. Reflexes were absent

in the right leg and hyperactive on the left side; the plantar response on the left was of extensor type. A myelogram demonstrated distortion of the spinal canal at the level of the thoracic spina bifida, and exploration of this area was advised.

At operation, the spina bifida was found to implicate the eighth, ninth and tenth thoracic spines; these formed a bony crater completely covering the spinal canal, which was enlarged at this level (fig. 2). At the same level the spinal cord was observed to be split at the dorsal median raphe. The bottom of the fissure, probably at or near the central canal, was covered by a nest of small blood vessels, the course of most of which paralleled the cord. From the lip of the fissure a film of thickened arachnoid united with the arachnoid and dura, separating the subarachnoid space into two parallel chambers. The dorsal roots followed this sheath and became lost in the fused arachnoid and dura, a modified "area granulosa." The rootlets and the thickened meninges were cut away.

The morning after operation the patient volunteered the information that he felt as though a great tension had been removed from his legs; objectively, movement of the legs seemed freer. Since operation our orthopedic colleagues have reported that there has been noteworthy improvement in rate and character of recovery.

In this case the original diagnosis had been spastic paraplegia, probably due to birth trauma. Before recognition of the scoliosis and spina bifida as potentially indicating the presence of demonstrable and relevant disease of the cord, efforts directed only toward correction of the paraplegic deformity had been notably unsucessful. At operation only the traction effect of the thickened arachnoid connecting the maldeveloped cord with its coverings was corrected. Apparently, this alone produced sufficient improvement in the activity of the lower segments to facilitate the initiation and maintenance of activity in the legs.

CASE 6.—*Hemangioma of the thoracic portion of the spinal cord, with intramedullary cyst of the lumbar enlargement.*

J. H. was first examined in April 1941, when, at the age of 23 months, it was noted that she limped and that she favored her right leg in walking. At that time she had a low grade fever but nothing else was noted in the course of a thorough examination. The family and past histories were irrelevant.

The child was followed closely, and two months after the first visit roentgenograms of the spine demonstrated what was interpreted to be a slight thoracic kyphoscoliosis with the convexity to the right. Physical therapy was directed toward correction of the limp. In October 1941, severe nocturnal abdominal pain accompanied with muscle spasm but not with tenderness, was the chief symptom. This condition subsided spontaneously over a six month period, during which, however, the scoliosis was noted to have progressed. A turnbuckle cast was applied.

From this time until January 1946, the child was seen by numerous physicians in various special fields because of recurrent bouts of abdominal pain with muscle spasm, because of the progressive scoliosis and, finally, because of progressive signs of disease of the spinal cord. In 1942 the Pandy test gave a positive reaction for globulin and the protein content of the cerebrospinal fluid was

90 mg. per hundred cubic centimeters, but there was no other sign of abnormality in the chemistry or the pressure of the cerebrospinal fluid. Further evidence of implication of the spinal cord appeared in 1943, when difficulty in urination was reported, and in 1945 progressive weakness of the right arm was noted.

In January 1946, there were weakness and atrophy of most of the muscles of the upper extremity, shoulder and thigh on the right side. Deep reflexes were absent at the knees and in the right arm, but there was sustained ankle clonus bilaterally, and the Babinski sign was elicited on both sides. Patchy loss

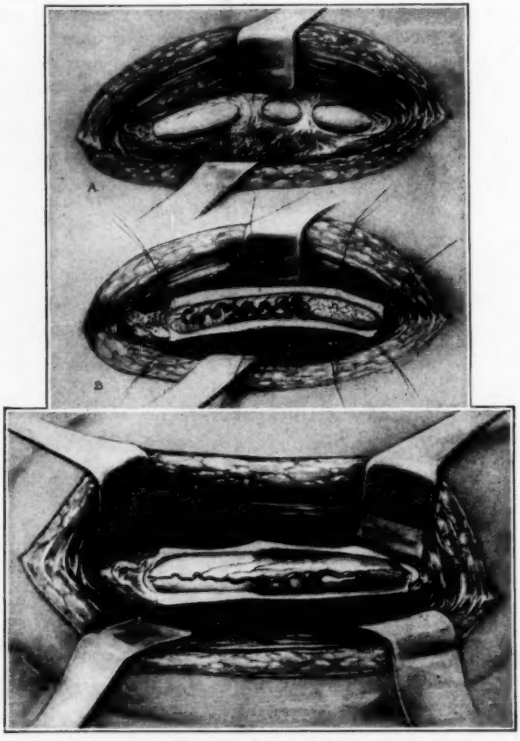

Fig. 3 (case 6).—*A*, curvature of the spine at the site of the vascular lesion, a curvature which was unaffected by a previous muscle-stripping procedure; *B*, angioma and intramedullary cyst in the lower thoracic and lumbar region; *C*, tapering of the angioma in the upper thoracic region.

of sensation from the third thoracic to the first lumbar dermatome was demonstrable. There was progressive loss of control of bladder and rectal sphincters. Xanthochromic fluid, which clotted on withdrawal, was obtained by lumbar puncture. At this time the evidence of disease of the spinal cord was interpreted as resulting from the severe degree of scoliosis together with subarchnoid adhesions.

In June 1946, the patient was seen at the Shriners' Hospital and was referred from there to the University of California Hospital for reevaluation of the

neurologic status. The child was found to hold her head in acute flexion, with chin on the chest. The legs were held in the fetal position by contractures and painful muscle spasm. Any variation from this position was extremely painful. The right arm and right thigh were weak; the muscles were atrophied. The bilateral sustained ankle clonus and Babinski response were still present. There was patchy, but definite, hypesthesia below the third thoracic dermatome.

At this time, during review of the previous roentgenograms, it was noted that the interpediculate spaces at the eighth, ninth and tenth thoracic segments were wide in the films taken in 1941 and in all succeeding ones. A myelogram accordingly was obtained, which demonstrated a complete block at the twelfth thoracic vertebra.

Operative treatment consisted of a two stage laminectomy which demonstrated a large angioma of the spinal canal extending from the first thoracic to the first lumbar segment (fig. 3). In the lumbar enlargement an intramedullary cyst was found, and the yellow fluid which it contained was evacuated. The entire thoracic portion of the dura was left open by way of decompression. After convalescence, orthopedic procedures to correct the flexion deformities and the scoliosis were resumed.

The clinical features of this case are similar to those of the case reported by Allen and Kahn.[1] In both cases the diagnosis was not established until a complete block appeared, and the development of neurologic symptoms subsequent to the onset of progressive scoliosis was for a time attributed to compression of the cord, contingent on the scoliosis. In this connection, it should be emphasized that even severe curvatures of the spine rarely interfere with function of the spinal cord, an observation made by Viets and Clifford.[2]

CASE 7.—*Thoracic angioma with scoliosis.*

B. A., a white boy aged 9 years, entered because of progressively increasing scoliosis of six years' duration.

The child's birth and development were normal, though he had had two serious gastrointestinal upsets before he was three years of age. After the second of these his parents first noted scoliosis. It was regarded as being due to generalized weakness, and a brace was prescribed for the back. At the age of 4 years clumsiness in use of the feet appeared, and six months later pain radiating into the lower part of the back and legs was reported. Successively, there followed urgency in urination, tickling in the soles of the feet, occasional drawing up of the feet and, throughout this period, progressive scoliosis. He was studied at the Shriners' Hospital and was referred from there for neurologic investigation. A family history of high arches in the mother and grandmother had been the basis for a diagnosis of Friedreich's ataxia.

The patient was a scrawny child; he presented moderate scoliosis, with convexity to the right, rather high pedal arches and a definite telangiectatic

1. Allen, S. S., and Kahn, E. A.: Case of Scoliosis Produced by Spinal Cord Tumor, J. Nerv. & Ment. Dis. **77**:53-55 (Jan.) 1933.

2. Viets, H. R., and Clifford, M. H.: Paraplegia Associated with Non-Tuberculous Kyphoscoliosis: Case Report and Survey of Literature, New England J. Med. **206**:55-61 (Jan. 14) 1932.

area on the left thigh. Café au lait spots were also present. There was moderate weakness of all movements of the legs, more evident on the left than on the right. The reflexes were underactive. The gait was clumsy but not ataxic. The Romberg sign was not elicited, and coordination when he was in the recumbent position was good. There was a definite reduction in sensitivity to pain below the general level of the fourth and fifth thoracic dermatomes bilaterally. The senses of joint position and vibration were intact.

Because of the progressive scoliosis and the telangiectatic mark on the thigh, the possible presence of an intraspinal angioma was entertained. Myelographic studies demonstrated widely dilated blood vessels on the dorsal surface of the thoracic portion of the cord at the site of the scoliosis, the main vessel being approximately one-third the diameter of the cord. A diagnosis of intraspinal angioma (thoracic) was made. In the absence of interference with the continuity of the subarachnoid space, operation was not recommended.

Friedreich's ataxia is one of the degenerative diseases with which scoliosis may be associated. In our opinion, however, the basis for such a diagnosis in this case is insufficient, whereas we were impressed by the vascular anomaly, which had been called angioma by the roentgenologists. Frequent reviews of the child's clinical status are planned so that any change indicating a positive approach to the vascular disease affecting the spinal cord itself may be recognized at the earliest possible time.

CASE 8.—*Thoracic angioma with scoliosis.*

R. W., an 8 year old white boy, was first seen in September 1947, because of "curvature of the spine." The history was that at the age of 1 month the patient had had an attack of "poliomyelitis" associated with a high fever and followed by complete quadriplegia of three months' duration. The patient regained motion of the extremities slowly over the ensuing months, during which time he was under constant treatment with braces. Scoliosis, which was the reason for referral, appeared at about the age of 2½ years and was reported to have become progressively worse in the ensuing period. He had been taken to the Shriners' Hospital at San Francisco and was referred from there for neurologic evaluation.

On examination, the striking abnormality was the pronounced scoliosis to the right in the upper thoracic region. Examination of the cranial nerves revealed no abnormality. Examination of the motor power demonstrated some weakness in the left arm and rather marked weakness in the right leg. Reflexes were active in all extremities, however, and the abdominal and cremasteric reflexes were present.

Myelograms with pantopaque® (ethyl iodophenylundecylate) showed a number of filling defects in the upper thoracic region. This was interpreted as representing an angioma in that region. Because there was no evidence of block, operation was not recommended, but the patient is being followed closely for evidences of involvement of the cord which might be of a remediable character.

In this case the question arises whether the original difficulty was a true poliomyelitis or whether there could have been bleeding at that time from the dilated vessels which have been demonstrated. Frank doubt as

to the diagnosis of poliomyelitis is entertained, and it is our opinion that the vascular changes demonstrated are related to the underlying cause of the scoliosis.

CASE 9.—*Cystic and adhesive arachnoiditis of unknown cause with scoliosis.*

M. de S., a 7 year old girl, was regarded as normal until the age of 5½ years, when "curvature of the spine" was first noted by the mother. Increasing deformity of the spine and rib cage was observed by the family in the succeeding months. The rest of the history, both personal and family, was irrelevant. The patient was referred from the San Francisco Shriners' Hospital for neurologic examination.

The patient was a thin child with a pronounced rotary scoliosis with the convexity to the right, extending from the fourth thoracic to the second lumbar vertebra. No atrophy of muscles was noted. The reflexes were somewhat hyperactive. There was a reduction of sensation to pain below the tenth thoracic level. The line of demarcation was broad, but the difference between somewhat separated areas (two to three segments) was consistent and convincing.

Myelograms were interpreted by the roentgenologist as demonstrating a "space-occupying lesion, most prominent at the fifth and sixth thoracic segments on the right, probably extramedullary."

This area was exposed surgically. The arachnoid was found to be thickened, and beneath it sheets of tissue connecting the spinal cord with the thickened arachnoid were encountered. Some of these sheets formed cystic loculations, which appeared to be intact and which distorted the cord by pressure of the fluid contained within them. Other sheets bound the cord to the adjacent meninges and interfered with the continuity of the subarachnoid channel. All these adhesions were interrupted, and the spinal cord was decompressed to eliminate reformation and a "water hammer" effect on the spinal cord.

After operation, orthopedic procedures directed toward mechanical correction of the scoliosis were resumed.

The cause of the adhesions in this case is obscure. Their density and extent were impressive, however; and their anatomic position such as would point strongly to relationship with the associated scoliosis.

CASE 10.—*Perineurial fibroblastoma of the left glossopharyngeal nerve with scoliosis.*

J. Y., a 14 year old Japanese girl, was admitted to the University of California Hospital in June 1946, because of a "crooked spine" associated with weakness, failure to gain weight and backache for the preceding two years. Two years previously, while apparently in excellent health, she suddenly fainted at school. There followed a year in which backache, failure to gain weight and generalized weakness were constant complaints. (During this time she was in a Japanese relocation center.) One year before admission her parents noticed the curvature of her spine, which was the reason for her referral to this hospital.

The past history and the family history were irrelevant.

The patient was a tall, slender girl. Her abdomen was flat and was held rigidly. There were a pronounced dorsal scoliosis and kyphosis, with the convexity to the right, and a compensatory lumbar scoliosis directed to the left. Some generalized wasting of the musculature was apparent. All movements of the back were limited to approximately one-fourth the normal range. Both

groups of hamstring muscles were spastic, and straight leg raising was limited to 30 degrees on the left and to 50 degrees on the right. The findings in the rest of the examination were considered normal.

Reactions to old tuberculin were negative in dilutions of 1:1,000 and 1:100. Roentgenographic examination of the spine confirmed the diagnosis of rotary scoliosis and showed widening of the lumbar interpedicular spaces, with scalloping on the anterior wall of the spinal canal, suggesting local compression, but failed to demonstrate any developmental anomalies or bony defects. The spinal fluid pressure was 460 mm. of water; the fluid was slightly xanthochromic; there were no cells; the Pandy test gave a 4 plus for albumin; the total pro-

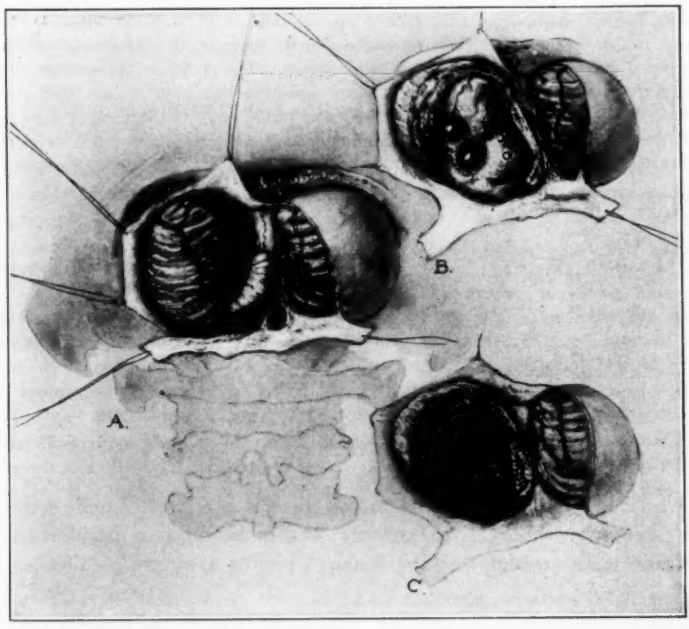

Fig. 4 (case 10).—The tumor producing the scoliosis lay at the jugular foramen. *A*, appearance of the tumor when first seen; *B*, the tumor after the overlying cerebellum had been removed; *C*, the cavity left after intracapsular removal of the growth at the first procedure. The entire mass was later extirpated, after a course of roentgen therapy had reduced the vascularity.

tein content was 500 mg. per hundred cubic centimeters. A myelogram taken with pantopaque® demonstrated enlargement of the spinal canal but no block or intraspinal mass.

Because of the increased spinal fluid pressure, ventriculographic study was advised. This revealed hydrocephalus with distortion and displacement of the aqueduct of Sylvius and of the fourth ventricle to the right. Considering this unexpected discovery, the patient was reexamined, but, again, no abnormality of any cranial nerve or of cerebellar function could be demonstrated. Only the pain in the patient's back was increased.

At operation, a large vascular tumor was observed to the left of, and just above, the foramen magnum (fig. 4). The brain stem was pushed to the right. Because of the extreme vascularity of the tumor, only a small biopsy specimen was taken. During postoperative convalescence the patient was given roentgen therapy in an attempt to reduce the vascularity preliminary to a second attempt at extirpation.

On her second admission the findings with respect to the back were unchanged. The suboccipital area of decompression was tense, and she exhibited unsteadiness, with a tendency to fall backward. In the interim visual acuity, also, had decreased considerably. The optic disks were pale, but there still was no papilledema. The left corneal reflex was diminished. There was palsy of the left facial nerve of peripheral type, and hearing was diminished in the left ear (nerve deafness). Nystagmus, coarse to the left and fine to the right, was present on extreme lateral gaze to either side. The gag reflex was diminished bilaterally. Deep reflexes were increased in the extremities of the left side.

At operation on this occasion the tumor was observed to fill the entire posterior fossa on the left and appeared to arise from the left glossopharyngeal nerve. It was possible to accomplish a complete removal by sacrificing the left ninth, tenth and eleventh cranial nerves. The tumor was a perineurial fibroblastoma. Since operation the scoliosis has not progressed further. Backache has improved, and considerable improvement in general feeling of well-being has occurred. Orthopedic measures to improve the spinal contour are being undertaken.

The course in this case is unusual. We have been greatly impressed, however, by the remarkable occurrence of the scoliosis long antedating the clinically demonstrable involvement of structures more generally considered to be affected early by growths in the posterior fossa. In this case, it even antedated the evidence of involvement of the nerve from which the growth arose. Scoliosis associated with tumors of the upper portion of the cord is common. A review of the history and findings in a series of 50 cases of involvement of the cervical and upper thoracic spinal cord by neoplasm revealed that scoliotic changes of a degree of diagnostic importance were present in 20 per cent. We are aware of no instance, however, in which the significance of scoliosis as a primary sign of such compression is more impressively shown than in the case just discussed.

COMMENT

The mechanism of scoliosis is beyond the scope of this paper. However, we have been impressed by the observation that when the site of compression of the cord seemed to be identifiable the convexity of the scoliotic curve was to the side of the affected pyramidal pathway. This supports the investigative work of Schwartzmann and Miles,[3] who

3. Schwartzmann, J. R., and Miles, M.: Experimental Production of Scoliosis in Rats and Mice, J. Bone & Joint Surg. **27**:59-69 (Jan.) 1945.

produced scoliosis with convexity to the weakened side by artificially produced paraspinal muscular imbalance.

We have found reference in the literature to scoliosis resulting from the various pathologic entities presented in the preceding section: Cobb,[4] Allen and Kahn,[1] and Ford [5] mentioned angiomas of the cord with scoliosis. In 4 of the 16 cases of tumor of the cord in children reported by Ingraham [6] scoliosis was present when the patient was first seen. Ray [7] noted the coincidence with platybasia, and Smith,[8] with transverse myelitis. Other related aspects were discussed by Kleinberg,[9] Bennett,[10] Wilson [11] and Viets and Clifford.[2]

To establish further the frequency of scoliosis as a manifestation of disease of the upper portion of the spinal cord, we reviewed a series of 60 cases in which disease of this location was established surgically. In these cases roentgenograms of the spine were available to show the presence or absence of scoliosis; there was usually a comment in the record as well. Scoliosis was found to have been present in 25 per cent of these cases.

Orthopedists have been increasingly aware of the possible relation of cause and effect between remediable disease of the spinal cord and scoliosis, and our orthopedic colleagues had given us the opportunity of studying many of the patients whose cases are reported here. The emphasis on such a relation in other fields of medicine, including that of disease of the nervous system, has been much less. Since it is oftenest orthopedists who see early scoliosis, it is well that there be recognition of related factors in their special field. The neurologist, however, must be sufficiently aware of the potentialities to be willing, as well as able, to render assistance in the pursuit of underlying causes.

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4. Cobb, S.: Haemangioma of the Spinal Cord Associated with Skin Naevi of the Same Metamere, Ann. Surg. **62**:641-649 (Dec.) 1915.

5. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1944.

6. Ingraham, F. D.: Intraspinal Tumors in Infancy and Childhood, Am. J. Surg. **39**:342-376 (Feb.) 1938.

7. Ray, B. S.: Platybasia with Involvement of Central Nervous System, Ann. Surg. **116**:231-250 (Aug.) 1942.

8. Smith, E. S.: Report of Case of Myelitis with Subsequent Deformity, Phys. Therap. **48**:499-507 (Oct.) 1930.

9. Kleinberg, S.: Structural Scoliosis Secondary to Syringomyelia: Report of Three Cases, J. Bone & Joint Surg. **15**:779-786 (July) 1933.

10. Bennett, G. E.: Tumors of Cauda Equina and Spinal Cord: Report of Four Cases in Which Marked Spasm of Erector Spinae and Hamstring Muscles Was Outstanding Sign, J. A. M. A. **89**:1480-1483 (Oct. 29) 1927.

11. Wilson, S. A. K.: Neurology, edited by A. N. Bruce, Baltimore, Williams & Wilkins Company, 1940.

This presentation has included only positive results. There have been many examinations of scoliotic patients, with and without clinically demonstrable neurologic abnormality, for whom all methods of neurologic examination short of actual inspection of the cord have yielded no information concerning the underlying etiologic factors. These patients, with scoliosis still "cryptogenic" or idiopathic," are being followed nonetheless, and repeated intensive reviews of their problems are contemplated.

The narcotic fallacy of unproved, but positively expressed, diagnosis is once more pointed up by the study of several of these patients, particularly those carried along with the diagnosis of poliomyelitis. In this series, cases erroneously classified under postpoliomyelitic scoliosis have run a close second in numbers to those of the frankly idiopathic type. The potential hazards to the patient are greater because of the sense of diagnostic security into which everyone is lulled by the satisfaction of a name.

SUMMARY AND CONCLUSION

Ten cases of disease of the cervicothoracic spinal cord in which scoliosis was the first, or an early principal, symptom are reported. Congenital anomalies involving the cord, cystic lesions of the cord, angioma, spinal varix, adhesions and extramedullary tumor constituted the underlying pathologic process.

It is to be emphasized that scoliosis may be an early, and at times the only, sign of a lesion of the cord. Attention to this fact may lead to surgical repair before irreversible changes take place.

Of a total of 60 consecutive surgically proved instances of cervical or upper thoracic lesion of the spinal cord, moderate to pronounced scoliosis was demonstrated in one fourth.

The convexity of the curve is usually toward the side of the lesion, when demonstrable, an observation in accord with results of experimentally produced scoliosis.

ABSTRACT OF DISCUSSION

DR. HENRY G. SCHWARTZ, St. Louis: The frequent occurrence of scoliosis with other signs of disease of the spinal cord is well known. The emphasis of Dr. Boldrey and his colleagues on recognition of scoliosis as an early or only sign will serve as a stimulus to salvage in a few cases of "idiopathic" or postpoliomyelitic spinal curvature. That they have collected 9 cases of scoliosis with definite lesions of the cord with a tumor of the angle is significant. Sporadic reports of isolated instances, such as that of Allen and Kahn, had appeared in the literature. Dr. Boldrey's series implies that the association of early scoliosis with tumor or vascular lesion is more frequent than can be accounted for on the basis of pure coincidence, an explanation which was Elsberg's. In this connection, it must be pointed out that of 2,000 cases of scoliosis studied by Ruhlin and Albert in Steindler's clinic, signs of involvement

of the cord developed in only 7, and in none was a tumor found; at operation, torsion of the cord secondary to scoliosis was the causative factor. Whether more widespread use of myelography is justifiable, with the hope that a few unrecognized tumors may be picked up, is a question which would be worth discussing with our orthopedic colleagues. A study of end results was made by the American Orthopedic Association several years ago. They concluded that the best method of treatment of idiopathic scoliosis was a combination of the turnbuckle cast and subsequent fusion. It is possible that if the cord were explored in cases selected for fusion, a few primary lesions might be found and the patients benefited. In the absence of other localizing signs, however, I doubt whether the apex of the curvature would bear any significant relation to the level of primary involvement of the cord.

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DESTRUCTION OF NERVE CELLS BY RICKETTSIAL ORGANISMS OF TSUTSUGAMUSHI FEVER

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TSUTSUGAMUSHI fever (scrub typhus) is a disease caused by Rickettsia nipponica (orientalis), which is transmitted to the human being from the bite of the larva of a trombiculid mite. From the site of the bite the organisms are carried by the blood stream to the leptomeninges and are distributed to the nerve cells of the central nervous system through endovascular cuffs. The meningeal distribution of the pathologic lesions in the central nervous system in 21 cases of tsutsugamushi fever (scrub typhus) was recently described by Weil and Haymaker.[1] They showed the pronounced cellular infiltration of the leptomeninges, perivascular spaces and choroid plexuses. Most of the reactive cells were histiocytes, together with some lymphocytes, plasma cells and other cells dislocated from the cortex. Nodules of microglia, which probably marked the earlier vascular invasion of the cerebral cortex, were illustrated. The present study was undertaken in order to show by a special method of staining the distribution of the rickettsias in the meninges, the cytoplasm of nerve cells and the perivascular cuffs and, furthermore, to show how the rickettsias destroyed the cytoplasm of nerve cells and how the organisms extruded from the nerve cells damaged the walls of the cerebral blood vessels. The material at hand clearly demonstrated the histopathology of vascular invasion, the ravaging of the Nissl substance and cytoplasm of the nerve cells and the perivascular collagenous changes in the walls of the cerebral blood vessels associated with the presence of rickettsial organisms.

MATERIALS AND METHODS

Several blocks of brain tissue, chiefly from the cerebral cortex of 2 human cases of tsutsugamushi fever in man were supplied by Dr. W. Haymaker, of the Army Institute of Pathology, Washington, D. C. It was known that the organisms of this

From Department of Zoology, Cornell University (Dr. Papez), and the Columbus State Hospital (Dr. Bateman).

1. Weil, A., and Haymaker, W.: The Distribution of the Pathologic Lesions of the Central Nervous System in Scrub Typhus, J. Neuropath. & Exper. Neurol. 5:271-284 (Oct.) 1946.

disease were resistant to most of the common stains, and that in the nerve cells they were demonstrated with difficulty, even with gram-negative stains, such as Giemsa's. With ordinary methods it was difficult to distinguish cytoplasm and Nissl substance from inclusion bodies and products of degeneration in the cytoplasm of nerve cells. To overcome these difficulties, a special stain was employed by one of us (J. W. P.)[2] Sections were cut 3 to 4 microns thick. This paper is concerned chiefly with demonstration of the intracytoplasmic rickettsias and their pathogenisis as revealed by this citric acid–sodium carbonate–cresyl violet stain.

The identity of the organism of human tsutsugamushi fever was established by comparing the sections with material from 2 mice inoculated intravenously with a 10 per cent yolk sac suspension of a lethal strain of R. nipponica. This material was prepared, stained and supplied by Capt. Thomas T. Crocker, department of virus and rickettsial diseases, Army Medical Center, Washington, D. C. He reported that on the sixth day after inoculation the mice were moribund and were chloroformed for autopsy. Both animals showed gross pathologic lesions typical of tsutsugamushi disease in mice. Before fixation, wet impression smears were made of the lung and spleen and of peritoneal scrapings and were stained by the Giemsa technic. The lungs of both mice were fixed in solution of formaldehyde U. S. P. (1:4), and sections were stained by us by a special method for inclusion bodies in nerve cells. All our studies were made with an oil immersion objective (× 120) and a × 10 eyepiece, giving a magnification of 1,200 diameters.

MICROSCOPIC OBSERVATIONS

In the smears of the mouse lung, the organisms of tsutsugamushi fever (R. nipponica) were clearly demonstrated. They were also seen in the smears of the spleen and in peritoneal scrapings. They appeared as numerous small, sharply defined bodies, located mostly in the cystoplasm of the cells. They stained as dots or as bipolar rods, readily distinguished by their blue or purple color, shape, size and disposition in relation to each other and to the cytoplasm of the tissues of the host. In figure 1, *1* and *2* are drawings of two cells from a smear of the mouse lung in which the rickettsias were seen as dots, often double or in groups of several organisms, and as bipolar rods, usually surrounded by clear halos. Sometimes the organisms were present in vacuoles in the cytoplasm; but oftener they were embedded in remnants of Nissl substance in the structural framework of the host cell, and the clear halos around them appeared to belong to them.

In the meninges in cases of human tsutsugamushi fever, the rickettsial organisms (fig. 1, *5* and fig. 2, *7*) were as apparent and characteristic as in the smears of organs of the mouse. They were seen as blue dots and bipolar rods in the cytoplasm of the histiocytes and of cells undetached from the lining of the leptomeningeal spaces. In figure 1, *5*, small groups of the rickettsias occur in histiocytes and meningeal cells. The organisms of tsutsugamushi fever in the human

2. Papez, J. W.: Neuronal Disease Associated with Intracytoplasmic Inclusion Bodies, Arch. Neurol. & Psychiat. **52**:217-229 (Sept.) 1944.

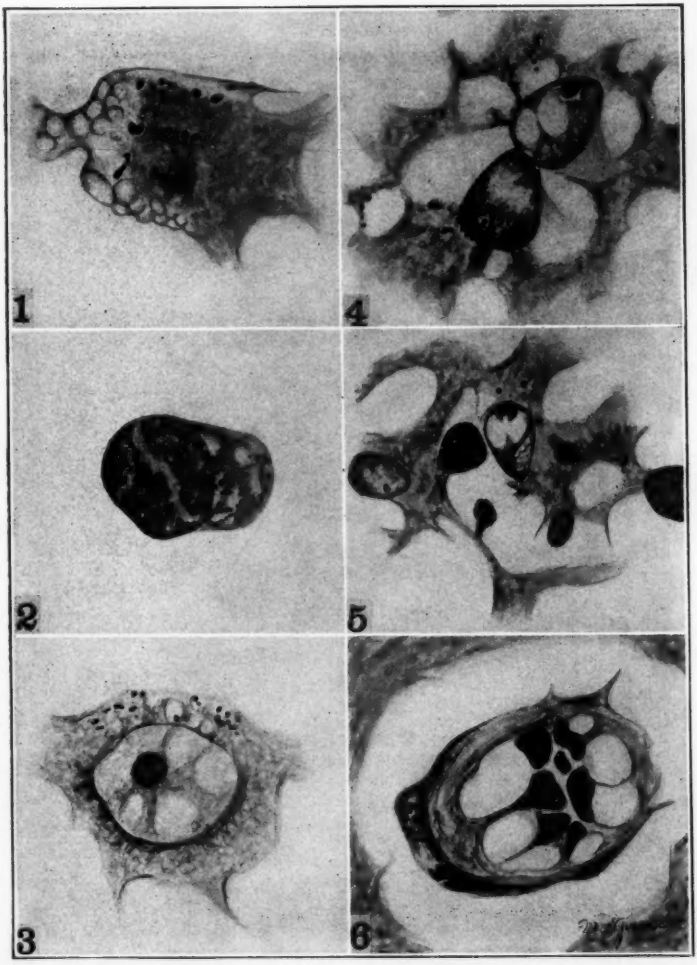

Fig. 1.—*1* and *2*, cells from a smear made of the lung of a mouse inoculated intravenously with a yolk sac suspension of Rickettsia nipponica (orientalis). The rickettsias are seen in the cytoplasm as black dots. Giemsa stain (Dr. T. T. Crocker); × 1,600.

3 to *6* are drawings of cells from the brain of a patient who died of tsutsugamushi fever. The special staining method devised by one of us (J. W. P.), citric acid, sodium carbonate and cresyl violet stain, was used.

3, nerve cell from the cortex. The rickettsias are seen in the cytoplasm as dots surrounded by clear rings. The cytoplasm is devoid of Nissl substance and appears somewhat honeycombed. × 1,600.

4, two nuclei of nerve cells stripped of their cytoplasm and surrounded by a network of intercellular substance, into which the rickettsias (seen as black dots) have been discharged. × 1,600.

5, section of leptomeninges showing rickettsias (seen as black dots and bipolar rods) in the cytoplasm of histiocytes and other meningeal cells. × 1,600.

6, cross section of an early stage of formation of a perivascular cuff in the wall of a small cerebral vessel. The rickettsias (seen as black dots) appear as partly degenerated inclusions in the cytoplasm of connective tissue cells. The lumen of the vessel is occupied by distorted red blood corpuscles. × 1,300.

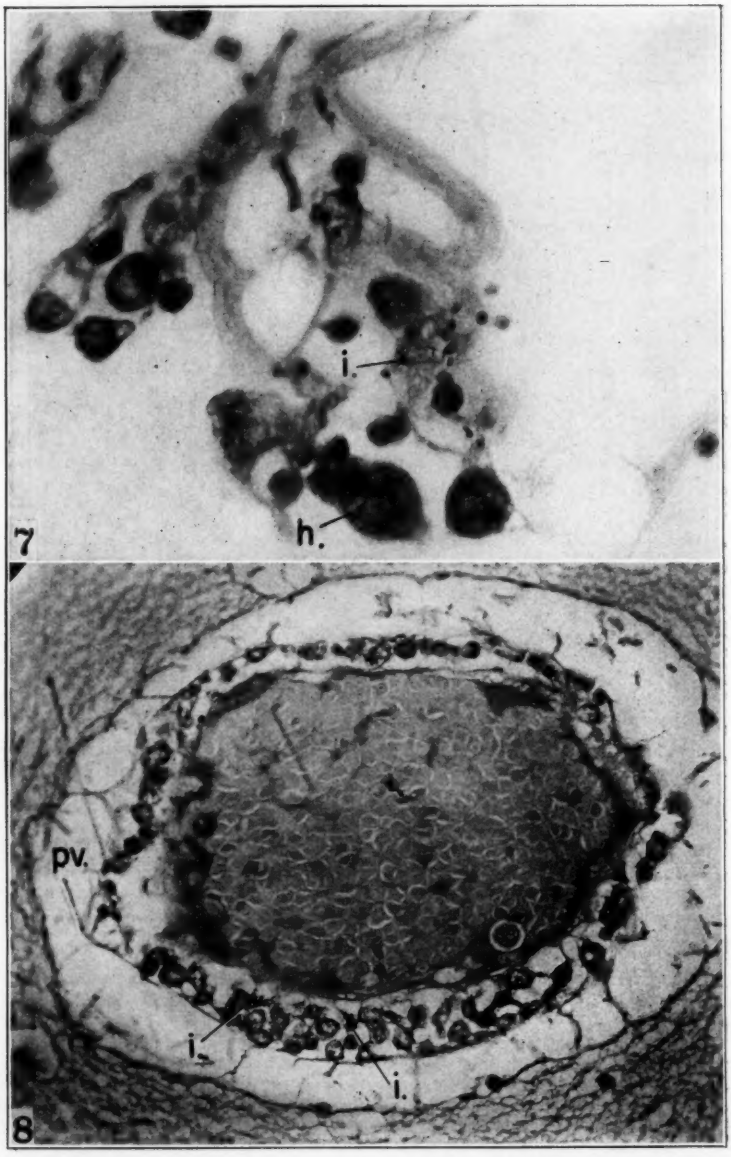

Fig. 2.—Photomicrographs of sections from the brain of a patient who died of tsutsugamushi fever. *7*, meninges showing histiocytes *(h)* and inclusion bodies *(i)* in the cytoplasm of meningeal cells. × 1,300.

8, large endovascular cuff, showing proliferation of endothelial cells and inclusion bodies (*i*) in their cytoplasm. The perivascular space is indicated by *pv*. × 470.

meninges as prepared by the special stain could not be distinguished from those in smears of mouse organs stained by the Giemsa method. Weil and Haymaker [1] have given good illustrations of the histopathologic picture of the leptomeninges and of the histiocytes. In figure 2, *7*, is a photomicrograph of the rickettsias as revealed in the meninges by the special stain employed in this study.

Endovascular cuffs were a peculiar feature, seen in the cerebral vessels in a few localities (fig. 2, *8*). The nuclei of the endothelial cells and other cells of the wall of the artery were increased in number. The cytoplasm of these cells was greatly expanded, partly honeycombed and broken down. A few organisms were noted in these histiocyte-like cells, and the appearance of the cells suggested that a large number of organisms had once been present in their cytoplasm. In a few places such invasion cuffs appeared to be related to the formation of microglial nodules. Settle, Pinkerton and Corbett [3] described the acute, generalized endothelioangiitis, vasculitis and perivasculitis which involved the vessels of most organs of the body in cases of tsutsugamushi disease. In the brain they described infrequent small nuclear nodules related to small blood vessels. The nodules consisted of irregularly placed mononuclear cells, microglia cells and occasional polymorphonuclear leukocytes. Lewthwaite and Savoor [4] stated that they saw rickettsias in the cells of the walls of the blood vessels. Allen and Spitz [5] and others presented microglial nodules associated with tsutsugamushi fever as characteristic features of the disease.

Staining of the rickettsial organisms in the nerve cells of the cerebral cortex offered difficulties. The ordinary cresyl violet stain applied to sections of this material did not reveal the organisms. In other sections prepared by the citric acid–sodium carbonate–cresyl violet method of Papez, [2] the rickettsial bodies stained pale to deep blue, while the cytoplasm of the nerve cells stained a bluish purple and the remnants of Nissl substance a pinkish violet. The nuclei of the nerve cells stained a dark blue or pinkish blue, and the nucleoli a deeper value of this color. For any one set of sections these color reactions remained fairly constant, but varied somewhat with changes in the staining procedure. The color reactions constituted one of the more important means of distinguishing the various elements in the histologic picture of tsutsugamushi infection of nerve cells.

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3. Settle, E. B.; Pinkerton, H., and Corbett, A. J.: A Pathologic Study of Tsutsugamushi Disease (Scrub Typhus) with Notes on Clinicopathologic Correlation, J. Lab. & Clin. Med. **30**:639-661 (Aug.) 1945.

4. Lewthwaite, R., and Savoor, S. R.: Typhus Group of Diseases in Malaya, Brit. J. Exper. Path. **17**:1-34 (Feb.) 1936.

5. Allen, A. C., and Spitz, S.: A Comparative Study of the Pathology of Scrub Typhus (Tsutsugamushi Disease) and Other Rickettsial Diseases, Am. J. Path. **21**:603-679 (July) 1945.

That the vital functions of the nerve cells were still intact, or were not severely impaired, was indicated by the condition of most of the nucleoli and nuclei. The nucleoli had the normal roundness and stained deeply. The surrounding chromatin material was represented by flat bands radiating from the nucleoli and spreading within the nuclear membrane. This appearance was fairly close to normal. However, the large clear fluid spaces (*f*) between the bands of nuclear chromatin indicated that abnormal changes were beginning in the nuclei of the nerve cells (fig. 3, *9* to *14*). Such fluid spaces often broke down the bands of chromatin. The fluid may represent protein.

The invasion and destruction of Nissl substance and cytoplasm of the nerve cells by rickettsias were conspicuous features of the cerebral cortex in cases of human tsutsugamushi fever. There was no doubt that the rickettsias destroyed the Nissl substance and reduced the cytoplasm of the nerve cells to a fenestrated network, or completely destroyed it. With the proper stain, the rickettsias were plainly seen as separate rods or dots, or as clusters in varius parts of the cell. At the stage of disease represented in these 2 cases, most of the organisms were in the cytoplasm or had been extruded. The intracellular habitat of these organisms was confirmed by hundreds of observations. Those seen in the outer walls of spaces around the nerve cells and in the intercellular network were apparently clusters previously extruded from disintegrated nerve cells (fig. 3, *14*). In figure 1, *3* is a drawing of a cortical cell infected with a small group of the organisms. In *4* of the same figure are shown the nuclei of two nerve cells whose cytoplasm has disintegrated, with discharge of the rickettsial organisms into their immediate surroundings. In *9* to *14* (fig. 3) are shown the presence of rickettsias as black dots in the cytoplasm, the progressive dissolution of the cytoplasm and its fusion with the surrounding network of intercellular substance.

The pathologic changes were a direct result of the invasion and partial destruction of the cytoplasm of most of the nerve cells of the cortex. Everywhere the cytoplasm of the cells was honeycombed and partly destroyed by the rickettsias. The organisms appeared to live in the spaces occupied by the blocks of Nissl substance. It was apparent that this substance was used up first, because most of the infected cells were devoid of it. When small flakes of Nissl substance remained, they were seen in the periphery of the cell body. This empty, and more or less vacuolated, cytoplasm of the nerve cells is shown in *9* to *14* of figure 3. Not all the cells contained the rickettsias, but it was apparent that most of them showed the same type of pathologic process. In many cells the rickettsias had already been discharged into the surrounding intercellular network. The organisms did not seem to be present in great numbers in any one cell.

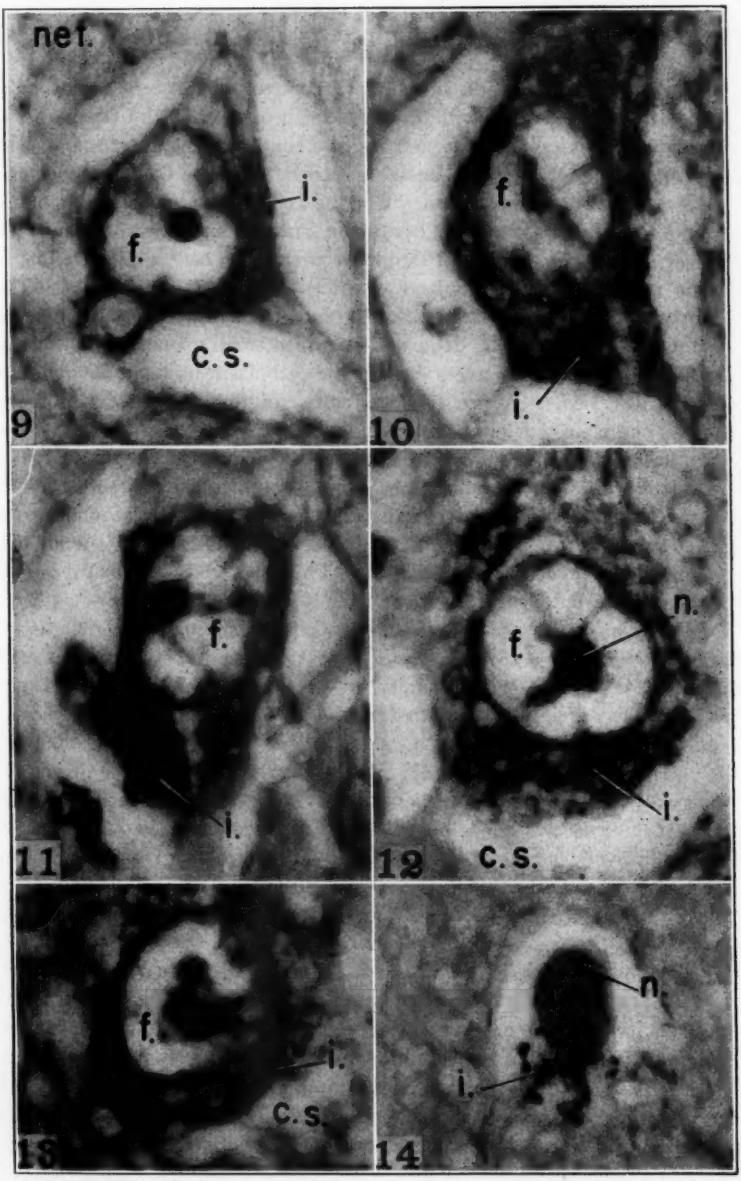

Fig. 3.—*9* to *13*, photomicrographs of individual nerve cells showing inclusion bodies *(i)* in their cytoplasm. The nucleoli *(n)* are intact. The clear fluid spaces *(f)* in the nucleus constitute the initial pathologic change which reflects cell disease. The cytoplasm is honeycombed, partially destroyed and fused with the intercellular network (*net*), as indicated in *13*, in which the cell space (*c. s.*) is lost. × 1,920.

14, naked nucleus of a nerve cell in which the cytoplasm has been destroyed and the inclusion bodies *(i)* have been discharged into the surrounding intercellular network. The nucleus and nucleolus *(n)* are atrophic and reduced in size. × 1,920.

In the process of dissolution of the cytoplasm of nerve cells, it looked as though the cytoplasm had been broken down by the parasitic (enzyme) activity of the rickettsias and that, at the same time, it was reformed into an intercellular network around the protoplasmic astrocytes. The cytoplasm of dissolving cells seemed to blend at many points by direct continuity with the surrounding intercellular substance (fig. 3, *13* and *14*). Dendrites seemed to have dissolved in the same manner. As a result, the spaces around the nerve cells (so clearly seen in normal tissue) were crossed by many strands; and some of the spaces occupied by dendrites contained small groups of rickettsias.

Nuclei survived complete lysis of the cytoplasm in about 20 per cent of the nerve cells. When the destruction of the cytoplasm was more or less complete, nuclei of nerve cells with remnants of cytoplasm were seen occupying the original cell spaces. Such surviving nuclei as a rule had lost their roundness and were compressed or distorted, with impoverished nucleoli and chromatin granules. The great abundance of such surviving nuclei of nerve cells, without axons or dendrites, indicated the severity of the disease. The small cells of cortical layers 2 and 3 were most severely affected.

It was apparent that cytolysis as a result of activity of the rickettsias, and not of phagocytosis, was the main process concerned in cell necrosis. Although protoplasmic astrocytes, and less frequently microglia cells, were closely associated with the destroyed neurons, phagocytosis of nerve cells was not in evidence.

The presence of microglia cells was determined by their small, irregular, darkly stained nuclei. These cells did not give evidence of phagocytic activity. The small, oval and somewhat vesicular nuclei of protoplasmic astrocytes were readily distinguished from the nuclei of nerve cells, with which they were closely associated. This satellitosis was related to the cytolysis and the formation of intercellular substance.

The intercellular substance was present in great quantity and formed a prominent feature of the diseased cortex (fig. *3, 9* to *14, net*). In fact, it made up the bulk of the cortical tissue, so that the cortex did not appear shrunken in spite of cellular destruction. The intercellular substance was arranged as an open, fenestrated network of protoplasmic bands and strands surrounding round fluid spaces. It appeared to be formed around the processes of the astrocytes. The great amount of intercellular substance was abnormal and was clearly related to the destructive disease of the nerve cells. Extrusion of the rickettsias into the intercellular substance was associated with dissolution of the surface of the cytoplasm. When discharged, the organisms occupied the outer part of the cell space or holes in the surrounding intercellular substance (fig. 3, *14*).

Migration of the discharged rickettsias to the blood vessels was apparently through the open spaces of the intercellular substances. The organisms were usually in aggregates, or in broken clumps held together by a membrane. These clumps were flattened and attached to the outer walls of the blood vessels. Figure 1, *6* illustrates a vessel with clumps of rickettsias flattened in its walls and embedded in the cytoplasm of the connective tissue cells. Although they were located on small and large blood vessels, they occurred frequently at points where the small veins joined the larger ones. They were present also in the walls of the larger arteries.

Perivascular cuffs were formed by increase in the cytoplasm of the connective tissue around the clumps of organisms. An early stage in cuff formation is shown in figure 1, *6*. The advanced stages of cuff formation were made of a fenestrated webbing of this perivascular tissue, enclosing irregular clumps of rickettsias in various stages of degeneration. This degeneration was readily recognized by the swelling, dark-staining and amorphous or ragged form of the rickettsias. The disorganized, pleomorphic appearance of the clumps was more frequent in the latter stages. The cuffs appeared to represent early stages in formation of sclerotic patches in the walls of the small veins and arteries, for in many places already devoid of rickettsias the cuffs presented a hyaline condition or a collagenous inflation. Almost every small blood vessel was affected by this type of perivasculitis. This picture is in agreement with Wolbach,[6] who gave a short description of such focal lesions in the cerebral cortex, thalamus, pons and cerebellum in 8 cases of tsutsugamushi fever. It was our impression that the degenerated organisms were removed by scavenger cells.

COMMENT

Staining of rickettsias in nerve tissues presented a number of difficulties because of the presence of Nissl substance in which the rickettsias were embedded and the presence of lipid in the more mature parasites. The hematoxylin and eosin stain was useless. Wolbach's modification of the Giemsa technic gave good results in other tissues.[7] We used a special citric acid–sodium carbonate–cresyl violet stain, which colored the rickettsias pale blue, distinct from color reactions of the components of the nerve tissue. With this method the Nissl substance was suppressed and the lipid removed, but ribodesoses stained well.

The staining characteristics varied, depending on the size and location of the organisms. The rickettsias of small size stained as pale

6. Wolbach, S. B.: Report on Microscopic Sections from Eight Cases of Scrub Typhus, cited by Ripley.[13]

7. Wolbach, S. W., in Harvard School of Public Health Symposium: Virus and Rickettsial Diseases, Cambridge, Mass., Harvard University Press, 1940, pp. 789-816.

dots or rods. The larger ones showed irregularities in contour and contained lipid. Those embedded in the walls of blood vessels usually showed granular swelling, dark staining and other signs of degeneration. Old degenerated forms appeared as formless degeneration products, but their rickettsial origin was recognized by their staining reaction in the perivascular cuffs, as well as in the gitter (scavenger) cells.

In the leptomeninges of human scrub typhus the rickettsial organisms stained distinctly. They appeared as bipolar rods and were similar to the tick-borne rickettsias as shown in photomicrographs by Bevan [8] and the inoculated mouse material which we used for identification.

Some endovascular cuffs with proliferating cells were present (fig. 2, *8*). There was evidence that they represented original points of massive invasion, as well as the points of origin of some of the microglia nodules.

In the nerve cells, of tsutsugamushi fever, the rickettsias were located in the webbing of the cytoplasm and in Nissl substance, from which they could be distinguished only with difficulty. This made photography difficult, and often unsatisfactory. The organisms tended to occur singly, close together or in clusters and colonies. In the nerve cell they were not always straight rods, some being bent to suit the contour of the cell. When single they were surrounded by a clear membrane or halo. In the compact clusters the membrane was not so apparent.

As nerve cells degenerated under the parasitic activity of the rickettsias, protoplasmic astrocytes clustered as satellites around the cell, and much intercellular substance was formed as a net between the cells. Some microglia cells were also present, but it was a question how much neuronophagia actually took place. The microglia cells seemed to be concerned later with removal of cell debris.

When the organisms were discharged from the nerve cell after disruption of the surface of the cytoplasm, the members of the rickettsial colony tended to become disarranged. Groups of the rod-shaped, and often bent, bodies lay across each other or were tangled at various angles, still tied together at some point by the membrane. This resulted in a remarkably confused, pleomorphic appearance of the discharged groups. Such tangled groups usually reached the walls of the blood vessels.

Perivascular cuffs (fig. 1, *6*) were quite different from the endovascular (invasion) cuffs (fig. 2, *8*). They were characterized by the great increase in collagenous tissue, arranged about the small blood

8. Bevan, C. DeV.: Cultivation of South African Rickettsiae in Developing Chicks and the Preparation of Vaccines from Their Membranes, South African J. M. Sc. **9**:1-20 (Feb.) 1944.

vessels as a loose, inflated cuff in which degenerating clumps of rickettsias were embedded. This perivasculitis has been described by most of the authors already referred to in this paper, as well as by Mendell [9] and Irons and Armstrong.[10]

That the rickettsias greatly impaired the functions of the nerve cells was apparent from the clinical histories of patients with tsutsugamushi fever. Sayen and associates,[11] in a clinical study of 616 cases, reported that the central nervous system was involved at least slightly in almost all cases. Machella and Forrester [12] noted mental symptoms in 9 of 64 cases. Ripley [13] reported neuropsychiatric signs and symptoms in 51 cases of tsutsugamushi fever. In several cases a true psychosis developed.

With the profound changes which have been reported in the brains of persons with rickettsial diseases, one may expect any and all types of neurologic and psychiatric disorders. Several thousand clinical cases have been reported by various authors. Nervous and mental disturbances have been mentioned in all these reports, the incidence ranging from 4 to 100 per cent.

From a psychiatric point of view, all the numerous symptoms described were those of an organic syndrome. Basically, there appeared mild gradations of "clouding of consciousness." Since there were so many mild transitory phases of this clouding, the symptom went unnoticed by those who were not particularly interested in the mental picture. However, Ripley,[13] in his series, found "impairment of cerebral functions in almost every patient." The symptoms described included all those common to the organic syndrome of clouding of consciousness. These symptoms ranged from the very mildest form, described in such terms as "things seem hazy," "in a mental fog," "inaccurate and incomplete grasp of the environment," to the more profound symptoms of cerebral involvement, such as delirium, stupor and coma.

Delirium, an advanced form of clouding of consciousness, comprised a miscellaneous group of symptoms, such as bewilderment, incoherence, disorientation, illusions, hallucinations and many transitory abnormalities, depending on the extent of the delirium. In stupor a more

9. Mendell, T. H.: Scrub Typhus Fever (Tsutsugamushi Disease) in New Guinea, Am. J. M. Sc. **211**:9-22 (Jan.) 1946.

10. Irons, E., and Armstrong, H.: Scrub Typhus in Dutch New Guinea, Ann. Int. Med. **26**:201-220 (Feb.) 1947.

11. Sayen, J. J.; Pond, H. S.; Forrester, J. S., and Wood, F. C.: Scrub Typhus in Assam and Burma, Medicine **25**:155-214 (May) 1946.

12. Machella, T. E., and Forrester, J. S.: Mite or Scrub Typhus: A Clinical and Laboratory Study of Sixty-Four Cases, Am. J. M. Sc. **210**:38-61 (July) 1945.

13. Ripley, H. S.: Neuropsychiatric Observations on Tsutsugamushi Fever (Scrub Typhus), Arch. Neurol. & Psychiat. **56**:42-54 (July) 1946.

pronounced dulling of the perceptive mechanisms was present, and, of course, in coma the impairment of consciousness was most profound, being present to such a degree that it was impossible to arouse the patient.

The aforedescribed symptoms were those of the classic psychiatric syndrome of organic type. Rickettsial disease produced this syndrome as a result of the toxic effect of the infection and the actual destruction of the Nissl substance and cytoplasm of the nerve cells. From the histologic picture of the disease, as presented in this paper, it was apparent that the nuclei and nucleoli were not so seriously impaired as was the cytoplasm of the nerve cells. It could be inferred that structural restoration of cytoplasm and recovery of cellular function were possible in a large number of the damaged cells which were not stripped of all their cytoplasm.

Rickettsial infection was not limited to the brain, but its effects on the blood vessels, heart muscle, renal glomeruli and other organs were profound. These somatic aspects of rickettsioses were discussed by Mendell [9] and elaborately illustrated by Allen and Spitz.[5]

A rapid heart beat and other signs of cardiovascular dysfunction were observed by Likoff [14] in 100 cases forty-nine days after the onset of the disease. Rapid heart beat or tachycardia at rest, dyspnea and precordial pain following exercise, and syncope were found in 30 per cent of the cases. Likoff inferred that the rickettsial disease might result in myocardial injury, although no evidence of cardiac failure or organic valvular disease was noted. In 10 of the 30 cases the electrocardiograms were abnormal. Sayen and associates [11] found myocardial changes at autopsy in all fatal cases of tsutsugamushi disease.

Serious involvement of the testes and the spermatogenic tissue of the seminiferous tubules was described by Allen and Spitz [5] in 36 cases. This observation deserves special mention because of a likely source of transmission to human offspring. It is quite possible that rickettsia infections transmitted in this way may result in the adaptation of a special variety of rickettsias to the central nervous system and the constitution of man.

Allen and Spitz [5] presented a pathologic concept of hyperergy in rickettsioses as including all the vascular and other irritative changes that rickettsias produce in various tissues of the body. They cited strong histologic evidence of altered tissue reactivity in cases of rickettsiosis. We have found that this altered tissue reactivity (as a noxious effect) is equally apparent in the brain, as shown by alterations in nerve cells (cytolysis); increased activity of astrocytes in forming intercellular substance; changes in the axons, myelin sheaths and oligodendroglia

14. Likoff, W.: Changes in the Cardiovascular System in Scrub Typhus in Early Convalescence, Am. J. M. Sc. **211**:694-700 (June) 1946.

cells; proliferation of oligodendroglia fibers, and formation of amyloid bodies, sclerotic plaques, perivascular cuffs and microglia nodules. These hyperergic effects may account for various functional aspects of nervous diseases due to rickettsias.

SUMMARY

The demonstration of the organisms of tsutsugamushi fever in the cytoplasm of nerve cells and in perivascular cuffs was achieved by use of a special citric acid–sodium carbonate–cresyl violet stain.

The rickettsias appeared as small bipolar rods, or as dots when they were seen on end. They stained a distinctive pale blue. They were identified by comparison with known cultures of R. nipponica propagated in the tissues of living mice.

In cases of tsutsugamushi fever in man the rickettsias were observed in the leptomeninges, in the endovascular cuffs and in the cytoplasm of nerve cells; when extruded from the nerve cells, they were seen in the network of intercellular substance. Organisms drifted to the small blood vessels and were embedded in the outer wall, forming perivascular cuffs characteristic of the disease.

In the nerve cell the rickettsias destroyed first the Nissl substance and then the cell body, leaving the nuclei stripped of cytoplasm. Such naked nuclei of nerve cells survived in great numbers.

The cytolysis or destruction of Nissl substance and cytoplasm depended on the presence of the rickettsias. As the cytoplasm was broken down, it appeared to be added to the network of intercellular substance. The abnormal amount of this network was characteristic of the pathologic process. The protoplasmic astrocytes seemed to be associated with the formation of this network. Some microglia cells were also present near the diseased nerve cells.

Endovascular (invasion) cuffs and microglial nodules were also present.

Rickettsial disease of cells of the brain is similar to, if not identical with, the inclusion bodies previously described in other forms of encephalomyelitis.[2]

Rickettsiosis is a disease of the entire organism, involving, sometimes selectively, major parts of the nervous system and, in addition, the blood vessels, heart muscle, renal glomeruli, testes and other organs. A mildly toxic substance is apparently produced which irritates neural, glial, vascular and collagenous tissues, cardiac muscle and other tissues of the body, leading to irreversible pathologic changes in the organs involved.

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PIAL-MEDULLARY ANGIOMAS

Clinicopathologic Features and Treatment

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AND

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THE OCCURRENCE of vascular anomalies of the central nervous system is well known and extensively treated in the literature. We are interested in presenting a discussion of those peculiar to the spinal cord and its most intimate covering, the pia-arachnoid.[1]

Nine cases are presented. We wish to show that these lesions can be suspected and diagnosed clinically on the basis of certain characteristic presenting features which in and of themselves may appear to be atypical. We wish, further, to point out that with the use of contrast roentgenography some of these lesions can be diagnosed with greater certainty before operation.[2] Recently an excellent work with particular reference to the number of cases reported (67) was compiled by Wyburn-Mason.[2d]

REPORT OF CASES

CASE 1.—A white man aged 27 was first admitted to the University Hospital on Jan. 30, 1938, with the questionable diagnosis of multiple sclerosis. His subjective complaints were those of weakness of both lower extremities and a staggering gait. The essential findings on examination were mild weakness of both lower extremities, with generalized hyperactive deep reflexes and extensor plantar responses bilaterally. There were some distal hypesthesia in the distribution of the first and second lumbar segments and diminution of appreciation of vibratory stimuli up to the level of the twelfth dorsal segment bilaterally.

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† Dr. Peet died March 25, 1949.

From the Departments of Surgery and Radiology, University of Michigan Medical School and the University Hospital.

1. Spiller, W. G., and Frazier, C. H.: Telangiectasis of the Spinal Cord, Arch. Neurol. & Psychiat. **10**:29-32 (July) 1923. Buchanan, D. N., and Walker, A. E.: Vascular Anomalies of the Spinal Cord in Children, Am. J. Dis. Child. **61**:928-932 (May) 1941.

2. (*a*) Bassett, R. C.: Diagnosis of Spinal Angiomas, University Hosp. Bull., Ann Arbor **12**:46-47 (May) 1946; (*b*) The Medullary Angiomas, abstracted, Surgery **20**:295-311 (Aug.) 1946. (*c*) Epstein, B. S., and Davidoff, L. M.: Roentgenological Diagnosis of Dilatation of the Spinal Cord Veins, Am. J. Roentgenol. **49**:476-479 (April) 1946. (*d*) Wyburn-Mason, R.: The Vascular Abnormalities and Tumors of the Spinal Cord and Its Membranes, St. Louis, C. V. Mosby Company, 1944.

Lumbar puncture disclosed no block. There were 20 crenated red blood cells per cubic millimeter. The fluid was not xanthochromic. Total protein measured 121 mg. per hundred cubic centimeters.

The patient left the hospital and returned six months later, at which time the findings were unchanged except that the total protein of the spinal fluid was 143 mg. per hundred cubic centimeters. Routine roentgenograms of the spine were normal. Myelographic studies disclosed what was interpreted as adhesive arachnoiditis at the level of the tenth and eleventh dorsal vertebrae (fig. 1).

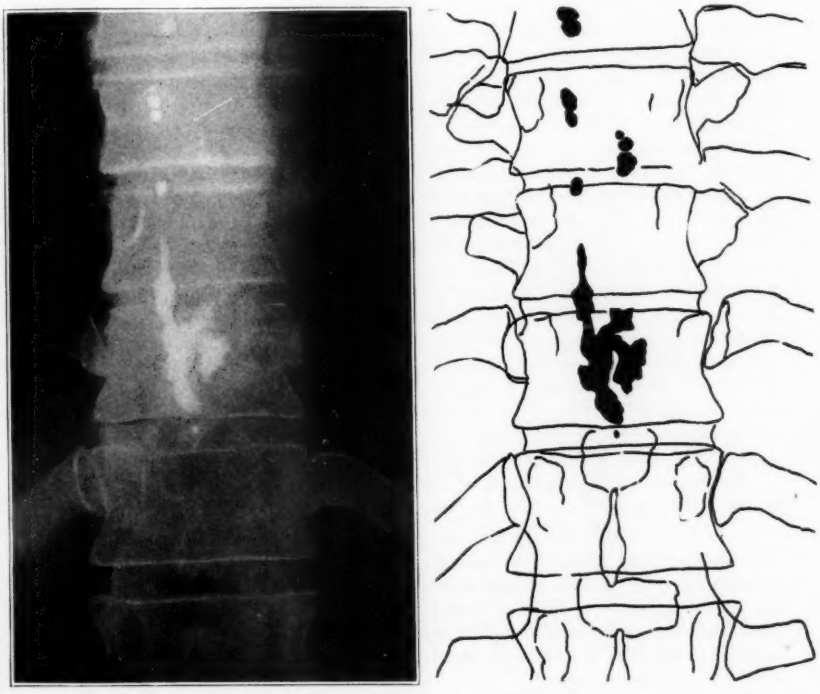

Fig. 1 (case 1).—Filling defect at the level of the tenth and eleventh thoracic segments and a highly irregular pattern of the oil column suggestive of adhesive arachnoiditis.

At operation a cirsoid angiomatous deformity of the dorsal surface of the cord and pia-arachnoid was disclosed at this level. The abnormal vessels were removed almost completely by ligation and section and coagulation.

Bilateral hyperactive knee and ankle jerks were the only residual signs one month after operation.

CASE 2.—A white man aged 63 was admitted to the University Hospital on June 24, 1941, with the questionable diagnosis of tumor of the spinal cord. The complaints on his admission were urinary retention, mild paraparesis of both lower extremities, severe radicular pain in both legs and an intense subjective sensation of coldness of the calves and feet.

Examination disclosed about equal weakness of the lower extremities, with foot drop on the left and an inactive knee jerk and a hyperactive ankle jerk bilaterally. There was total absence of vibratory sensation up to the iliac crest on both sides. Roentgenograms of the spine made elsewhere revealed nothing of significance. Myelographic studies were not undertaken. Spinal puncture was not done.

Operation disclosed an angiomatous lesion involving the conus and upper segments of the cauda equina. All abnormal extramedullary vessels were removed.

Eighteen months after operation the findings were unchanged.

CASE 3.—A white woman aged 21 was admitted to the University Hospital on Nov. 6, 1942, with the tentative diagnosis of multiple sclerosis. The primary complaint was loss of motion and position sense of the right hand, having its onset two years before admission. The condition had progressed to almost complete paralysis. Six months before her admission similar signs involved the left hand and arm. Two and one-half months previous to admission there were onset of weakness of both lower extremities and progressive difficulty in swallowing.

Examination disclosed spastic tetraparesis. There were dissociated sensory findings with loss of temperature and pain sense but preservation of tactile sense in a band from the third cervical to the first thoracic segment bilaterally. There were no sensory changes in the lower extremities except for diminished appreciation of vibratory sensation in the left leg to the level of the iliac crest. Routine roentgenograms of the spine were noncontributory. Spinal puncture disclosed a total protein of 1,500 mg. per hundred cubic centimeters. There was no record of manometric procedures. Myelographic studies disclosed an obstructive lesion in the cervicodorsal region, which was interpreted as an intramedullary tumor.

Operation revealed a "hemangioma" extending from the third cervical segment to the level of the foramen magnum. The cervical portion of the cord was conspicuously enlarged caudally to about the seventh cervical segment. After operation a course of high voltage roentgen ray therapy, totaling 2,600 r, was given to a portal covering the posterior fossa and the cervical portion of the spine.

The patient had tetraparesis after operation and when she was last heard from, five months later, her condition was unchanged.

CASE 4.—A white man aged 41 was first admitted to the University Hospital on Feb. 11, 1943, having been studied elsewhere. Diagnoses of poliomyelitis, the Guillain-Barré syndrome, amyotrophic lateral sclerosis and alcoholic neuritis had all been entertained as possible causes of the patient's difficulty. The presenting complaints were weakness of and severe radicular pain in both lower extremities, which had begun in the right leg about six months prior to his admission and had gradually become bilateral.

Examination disclosed paraparesis, the paresis being greater on the left side than on the right. Complete foot drop was present on the left. There was bizarre sensory dissociation of all modalities to the level of the first lumbar segment on the right and to the third lumbar segment on the left. Lumbar puncture disclosed no block, and the fluid contained no red cells and was not xanthochromic. The total protein was 91 mg. per hundred cubic centimeters.

Routine roentgenograms of the spine were noncontributory. Myelographic studies disclosed what was interpreted to be minimal arachnoiditis at the level of the eleventh and twelfth thoracic vertebrae.

At operation a cirsoid angiomatous anomaly, extending from two or three segments above the conus into the cauda equina at the level of the third lumbar vertebra, was disclosed. The pathologic vessels were removed practically *in toto*. Arachnoidal cicatrices were destroyed by lysis. After operation, the patient

received high voltage roentgen ray therapy to a portal centering over the laminectomy scar, a total dose of 3,000 r being administered.

Eleven months after operation there was minimal improvement in dorsiflexion of the feet. The neurologic status otherwise remained the same. The patient had persistent intermittent stabbing radicular pain in both lower extremities.

CASE 5.—A white man aged 57 was admitted to the University Hospital on July 19, 1944, with the tentative diagnosis of prostatic obstruction, an "acute abdomen" and possible poliomyelitis. He had had onset of severe pain in the lower part of the abdomen about ten months before admission, associated with urinary

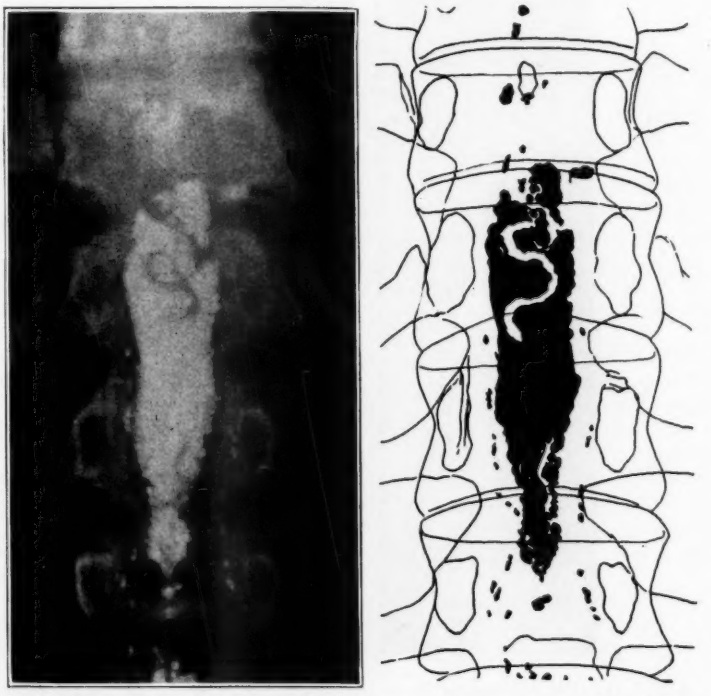

Fig. 2 (case 5).—Typical irregular block to the flow of oil at the eleventh thoracic segment and a sinusoidal shadow characteristic of the anomalous vessels.

retention, which gradually changed to total incontinence, and gradual development of weakness of both lower extremities.

Examination disclosed rather severe paraparesis with associated patchy atrophy of the lower extremities. There were bilateral ataxia, steppage gait and bilateral signs referable to the pyramidal tracts. Spinal puncture was not performed, since oil had previously been placed in the subarachnoid space while the patient was in another hospital.

Roentgenograms of the spine made elsewhere showed nothing abnormal. Myelographic studies revealed a partial block at the level of the eleventh and twelfth thoracic vertebrae, and a spiral area of decreased density seen throughout the oil column suggested a dilated blood vessel (fig. 2).

Operation revealed a cirsoid angiomatous anomaly, for the most part intramedullary, involving the conus primarily and extending into the cauda equina.

The patient died on his one hundred and first day in the hospital, of urinary sepsis and renal failure. There had been no change in his neurologic status.

CASE 6.—A white woman aged 26 was admitted to the University Hospital on Nov. 15, 1944, with a disorder of thirteen months' duration. The onset was with pain between the shoulders and paresthesias in both arms, associated with flexion of the neck. Ten months previous to her admission minimal weakness of

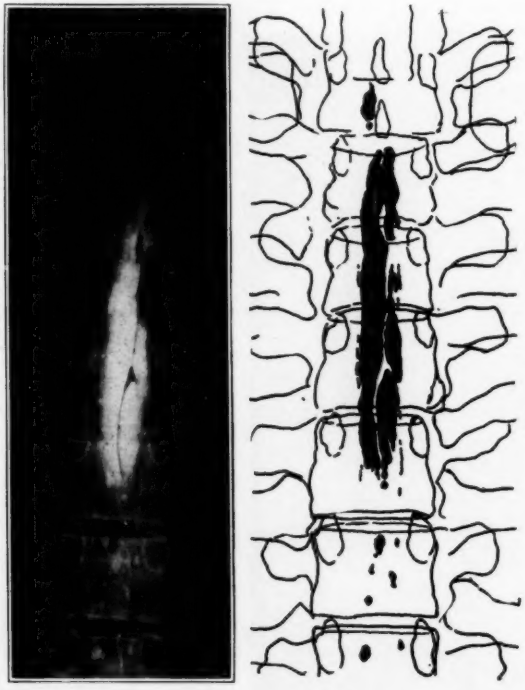

Fig. 3 (case 6).—Irregular linear changes in density in the oil column extending from the first to the fifth thoracic segment.

both lower extremities developed, and four months prior to admission she had gradual onset of incontinence of the bladder and bowel which was progressive.

Examination disclosed a level for loss of appreciation of temperature, pain and light tactile sensation at the seventh dorsal segment bilaterally. There were minimal paraparesis of the lower extremities and bilateral signs of involvement of the pyramidal tract. Lumbar puncture disclosed no block. The total protein was 55 mg. per hundred cubic centimeters.

Routine roentgenograms of the spine were noncontributory. Myelographic studies were interpreted as showing a "hemangioma" at the level of the third thoracic vertebra (fig. 3.)

Operation revealed a predominantly intramedullary angiomatous lesion at the level of the third thoracic vertebra.

After operation the patient was given high voltage roentgen therapy, totaling 2,400 r, to a field centered over the healed laminectomy scar.

During a postoperative period of seven months there were progressive weakness of both lower extremities and progressive loss of bowel and bladder control. The patient was then given further radiation therapy by her home physician, a total dose of 2,200 r being administered to each of two portals above and below the site of previous irradiation.

The patient returned on Sept. 27, 1945, with the complaint of further progression of the diplegia of the lower extremities and the bowel and bladder incontinence. In addition, there had developed shooting paresthesias into both arms, particularly accentuated with flexion of the head and neck.

Myelographic examination disclosed an incomplete block, beginning at the level of the sixth thoracic intervertebral disk space.

On October 4, the previous operative site was reopened, disclosing dense, plastic, white fibrous arachnoiditis with multiple cicatrices strangulating the spinal cord. These adhesions were freed as much as possible. It was felt that the pathologic condition was probably a result of the heavy radiation therapy.

Three months after operation her subjective and objective status was unchanged.

CASE 6.—A white man aged 38 was first admitted to the University Hospital on May 23, 1945, with the tentative diagnosis of peptic ulcer associated with duodenal diverticulitis. He had a five year history of intermittent severe pain in the right costovertebral angle, radiating anteriorly. One week previous to admission he had experienced a similar sort of pain in the left hip.

Examination disclosed only absence of the knee jerk on the left side and minimal weakness of the extensor hallucis longus on the left. Lumbar puncture revealed no block. There were no cells. The fluid was normal in color. The total protein was 32 mg. per hundred cubic centimeters.

Roentgenograms of the spine showed nothing significant. Myelographic studies disclosed a filling defect between the twelfth thoracic and the first lumbar vertebra on the left, the lesion being interpreted as a possible extramedullary tumor.

At operation an angiomatous mass on the dorsal and right lateral surfaces of the cord, extending from the tenth to the eleventh vertebral level, was disclosed and removed practically *in toto*.

Five months after operation the patient was asymptomatic except for occasional radicular pain in the right calf and an area of hypesthesia the size of a palm on the posterior surface of the right calf.

CASE 7.—A white man aged 39 was first admitted to the University Hospital on Dec. 20, 1945, with the tentative diagnosis of multiple sclerosis and a four months' progressive history of pain in the lower part of the back, loss of bladder function and sexual impotency, numbness and tingling, weakness and ataxia of the lower extremities.

Primary neurologic findings were moderate atrophy of the muscles of the thigh, particularly on the right, and diminished muscular tone in both lower extremities, the paresis being greater on the left. Pronounced ataxia was evident in the heel to knee to toe test bilaterally. The lower abdominal and the cremasteric reflexes were absent bilaterally. The knee jerks were equally hyperactive on the two sides, and both ankle jerks were absent. There was diminution of all forms of sensation below the twelfth thoracic level on the right and the first lumbar segment on the left, the sensory loss increasing distally. Cystometric examination demonstrated an atonic, neurogenic bladder. Lumbar puncture dis-

closed clear and colorless fluid, a partial dynamic block, with a slow fall after jugular compression, no cells, and a total protein of 174 mg. per hundred cubic centimeters.

Roentgenograms of the spine showed nothing abnormal. Myelographic examination with pantopaque® (ethyl iodophenylundecylate) disclosed an incomplete filling defect, predominantly on the left side, at the level of the tenth and eleventh thoracic segments (fig. 4).

On Feb. 1, 1946 a typical "angle-worm" deformity of abnormal vessels was removed *in toto*.

Postoperative improvement was gradual until, at the end of three months, the only deficit was mild saddle hypesthesia, continued absence of bladder sensation

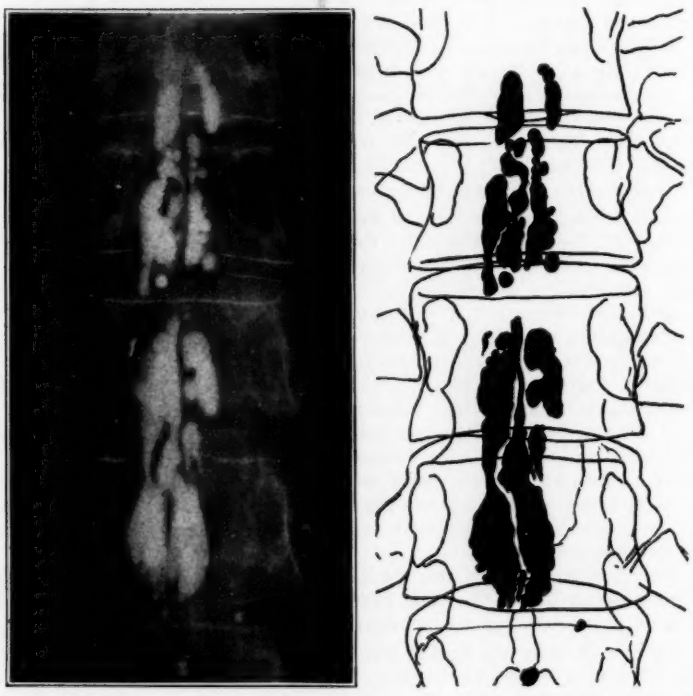

Fig. 4 (case 7).—Oil pattern characteristic of the linear changes in density produced by anomalous vessels in the lower part of the cord and the cauda equina.

to heat and cold but return of sensation of filling and distention. The residual urine measured only 45 cc.

CASE 8.—A white woman aged 45 was admitted to the University Hospital on Jan. 17, 1946, with the history of gradual development over a period of three years of spastic paralysis of both lower extremities, beginning in the right leg. She had been confined to bed for one year prior to admission. She had no control of bowel or bladder function.

The chief findings were pronounced spastic paraplegia and associated massive defense flexion movements of the lower extremities, reflex neurogenic bladder

with preservation of temperature sensation, hypesthesia for tactile stimuli to the tenth thoracic dermatome on the right and the twelfth thoracic dermatome on the left, loss of pain and temperature sense in the right lower extremity to the midthigh, absence of abdominal reflexes in all four quadrants and marked dorsiflexion on plantar stimulation bilaterally. Roentgenograms of the spine were not helpful. A myelographic study with pantopaque® revealed a lesion suspected to be made up of abnormal blood vessels which extended from the cervicothoracic junction to the midthoracic region (fig. 5). Lumbar puncture revealed normal pressure, dynamic status and cell content. The total protein content of the cerebrospinal fluid was 65 mg. per hundred cubic centimeters.

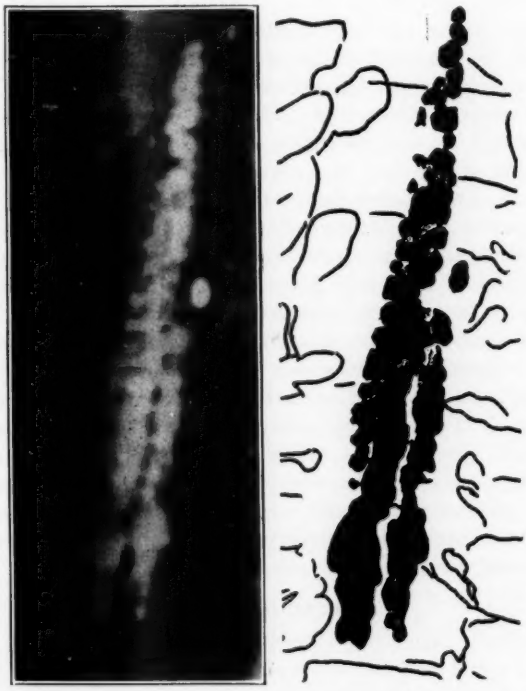

Fig. 5 (case 8).—Typical changes in the linear densities within the oil column produced by anomalous vessels.

At operation (first to second thoracic segment) a predominantly intramedullary angioma was disclosed and not disturbed.

Sensation and bladder function had returned fourteen months later; however, the marked spastic paraplegia with mass flexion movements persisted.

COMMENT

The extradural and vertebral hemangiomas are readily recognized, owing to their more definitive signs of localizing compression of the cord and the readiness with which they may be visualized in roentgeno-

grams.[3] On the other hand, the angiomatous anomalies of the pia-arachnoid and the spinal cord characteristically present a less clear picture.[4]

The onset of the clinical picture is most frequently sudden, often, though not always, the result of subarachnoid hemorrhage, and the symptoms may be intermittent. Pain in the back corresponding to the level of the lesion, which at first may or may not have radicular components, is usual. The lesions situated in the lower thoracic portion of the cord, the conus and the cauda equina are quite constantly associated with radicular pain in the lower extremities out of all proportion to the objective signs. Pain of sudden onset occurs with rupture of one or more of the abnormal vessels or as a result of changes in intrathecal tension, causing changes in position of these structures with production of compression of nerve roots. Residual discomfort is the result of organization, with scar formation (following hemorrhage), producing strangulation of the cord and nerve roots. It is at this point in the development of the clinical picture that profound objective signs become evident—bizarre and segmentally incompatible sensory, motor and visceral phenomena in the sense of a single focal lesion or process.

The objective signs may appear unassociated with pain, especially in cases of predominantly intramedullary lesions; however, pain may be the first symptom,[5] with or without minimal findings. The evidence is usually suggestive of a long, but incomplete, lesion. The low thoracic and lumbar segments of the cord are the parts most often affected.

As a result of the seeming incongruity of the subjective and objective clinical signs, these lesions are almost routinely misdiagnosed early. Poliomyelitis; multiple sclerosis; other inflammatory and degenerative myelitides and neuritides, and, not uncommonly, gastrointestinal disorders, such as peptic ulcer, cholecystitis and diverticulitis, are the most frequent initial diagnoses.

ROENTGENOLOGIC CHANGES

The typically suggestive myelographic changes produced by dilated veins in the spinal cord and its coverings have previously been described.[6]

3. Ferber, L., and Lampe, I.: Hemangioma of Vertebra Associated with Compression of the Cord, Arch. Neurol. & Psychiat. **47**:19-29 (Jan.) 1942. Globus, J. H., and Doshay, L. J.: Venous Dilatations, with Signs and Symptoms of Cord Compression, Surg., Gynec. & Obst. **48**:345-365 (March) 1929.

4. (*a*) Adson, A. W., and Ott, W. O.: Results of the Removal of Tumors of the Spinal Cord, Arch. Neurol. & Psychiat. **8**:520-537 (Nov.) 1922. (*b*) Bassett.[2a] (*c*) Wyburn-Mason.[2d]

5. (*a*) Adson and Ott.[4a] (*b*) Blahd, M. E.: Hemangioma of the Spinal Cord, J. A. M. A. **80**:1452-1453 (May 19) 1923. (*c*) Cobb, S.: Hemangioma of the Spinal Cord, Ann. Surg. **62**:641-649 (Dec. 15) 1926.

6. Bassett.[2a] Epstein and Dandoff.[2c] Cushing, H., and Bailey, P.: Tumors Arising from Blood-Vessels of the Brain, Springfield, Ill., Charles C Thomas, Publisher, 1928.

It was not until our attention was called to the startling sigmoid deformity shown in figure 2 that we reviewed the roentgenograms in preceding cases in which myelographic studies had been made and in retrospect interpreted the findings in a more positive manner. Prior to recognition of the characteristic roentgenologic picture created by these lesions, the presence of such angiomatous deformities remained a matter of clinical conjecture.

During the myelographic procedure the oil is dispersed and broken up into columns which follow the topography of the angiomatous mass on the cord and pial surfaces (figs. 1, 2, 3 and 4). When well defined wormlike filling defects are seen in the column of opaque medium, a diagnosis of pial-medullary angioma can be made with reasonable certainty. When this characteristic appearance is lacking, one must be careful to avoid misinterpreting a fortuitous arrangement of oil droplets or the delicate longitudinal striations of normal blood vessels as evidence of an abnormal vascular pattern.

Only rarely do these angiomatous malformations obstruct the flow of opaque medium in the neural canal so completely as to suggest the presence of a more discrete extramedullary space-occupying lesion. Perhaps the chief differential diagnostic problem presented by the myelogram is that of adhesive arachnoiditis, with its multiple deformities due to pseudocysts and cicatrices. The latter picture is not uncommonly superimposed on that created by the angiomas as a result of organizing hemorrhage from one or more ruptured anomalous vessels.

PATHOLOGY

Grossly, these lesions have the appearance suggestive of a mass of earthworms,[4c] presenting a tangle of pulsating vessels of widely varying diameter and length. There may be one or more, usually three, large vessels up to 4 or 5 mm. in diameter, the greater number varying from 1 to 2 mm. in diameter. Frequently there is an associated cicatricial or pseudocystic arachnoiditis, the result of organizing hemorrhage following rupture of one or more varices of the mass.

Histologically these vessels are unimpressive, showing only wide variation in structure of the walls. The lumens vary in diameter according to the mural structure, which may simply show cavernous angiomatous dilatation, limited by a thin endothelial and fibroadventitious layer, or may exhibit more thickened, arterial-like construction.

THERAPY

The treatment of these lesions is surgical removal. Ligation and piecemeal removal of the larger vascular elements [7] and cautious electro-

7. Elsberg, C. A.: Surgical Significance: Varicose Veins of the Spinal Cord, Am. J. M. Sc. **151**:642-652 (April) 1916. Bassett.[2b]

coagulation of the remaining vessels are carried out as extensively as possible. Frequently the predominant portion of the mass of vessels may be almost entirely intramedullary. No attempt at palliative decompressive myelotomy should be made, since the brisk hemorrhage which may ensue could bring about more extensive and irreversible damage to the cord than was present before operation. In such cases the dura may be allowed to remain open for decompression. It is also to be remembered that the cord distal to the abnormal vessels may be to a great extent dependent on one or more of these structures for a good share of its blood supply. However, we believe that consideration of this possible objection to as total therapy as possible is dependent on individual judgment and experience. In all our cases, total ligation, coagulation and removal were done when the lesion was predominantly extramedullary—with improvement in all. In those cases in which little or no postoperative improvement occurred, the lesions were predominantly intramedullary, or there were extensive cicatricial arachnoidal adhesions of long standing.

High voltage roentgen therapy is recommended by some when wound healing is well established. Whether any therapeutic effect is actually induced by irradiation we are not prepared to state. It may be that by this means sclerosis and thrombosis of the abnormal structures will occur, but it must be borne in mind that normal vessels in the spinal cord may be adversely affected by irradiation sufficient to destroy the abnormal vessels in this type of angioma.

SUMMARY

Nine cases of angiomatous lesions of the spinal cord and the spinal pia-arachnoid are presented and discussed according to their clinicopathologic and roentgenographic characteristics.

The presence of these lesions can usually be suspected clinically and the diagnosis frequently confirmed by roentgenographic technics employing contrast myelography.

Treatment consists in surgical removal of as many of the abnormal vessels as possible. Decompressive myelotomy in instances in which the lesion is predominantly intramedullary is not recommended.

Dr. Guillermo Santin, of the Hospital Frances, México, D. F. Mexico, prepared the diagrams as an aid in interpreting the roentgenograms.

University Hospital.

RELATION OF CHANGES IN CARBOHYDRATE METABOLISM TO PSYCHOTIC STATES

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PREVIOUS investigations [1] have shown a tendency to a disorder in carbohydrate metabolism associated with the psychoses, chiefly in the nature of reduced sugar tolerance. The cause of this dysfunction has been obscure and has been attributed to various factors, including poor absorption from the gastrointestinal tract, marginal malnutrition [2] and delay in insulin reaction.[1a] Our studies at the Worcester State Hospital have suggested that the reduced glucose tolerance is related in some way to the emotional tension. In confirmation of this hypothesis, we were able to produce a reduction in the glucose tolerance by means of a psycholologic stress situation.[1b]

In an attempt to clarify the relation of the glucose tolerance to the psychiatric status, we undertook a study of the sugar tolerance in relation to changes in the patient induced primarily by electric shock therapy. Previous reports by Diethelm [3] with regard to spontaneous variations in the patient and by Proctor, Dewan and McNeel [4] concerning changes following insulin shock therapy have suggested that improvement in the mental status is usually accompanied with an increase in the glucose tolerance, i. e., a trend toward normality.

Read before the Boston Society of Psychiatry and Neurology, Oct. 18, 1945.

From the Memorial Foundation for Neuro-Endocrine Research and the Research Service of the Worcester State Hospital.

1. (*a*) Braceland, F. J.; Meduna, L. J., and Vaichulis, J. A.: Delayed Action of Insulin in Schizophrenia, Am. J. Psychiat. **102**:108-110, 1945. (*b*) Freeman, H.; Rodnick, E. H.; Shakow, D., and Lebeaux, T.: The Carbohydrate Tolerance of Mentally Disturbed Soldiers, Psychosom. Med. **6**:311-317, 1944.

2. Robinson, G. W., and Shelton, P.: Incidence and Interpretation of Diabetic-Like Dextrose Tolerance Curves in Nervous and Mental Patients, J. A. M. A. **114**:2279-2284 (June 8) 1940.

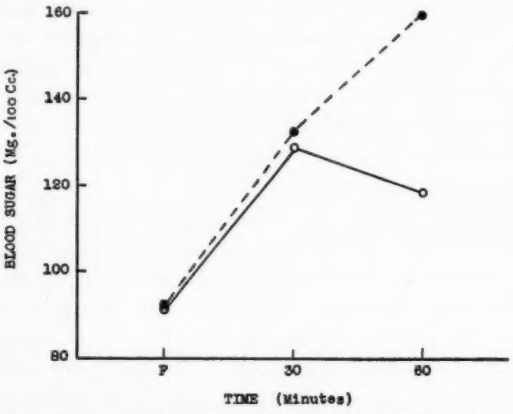
3. Diethelm, O.: Influence of Emotions on Dextrose Tolerance, Arch. Neurol. & Psychiat. **36**:342-361 (Aug.) 1936.

4. Proctor, L. M.; Dewan, J. G., and McNeel, B. H.: Variations in Glucose Tolerance Observations in Schizophrenics Before and After Shock Treatment, Am. J. Psychiat. **100**:652-658, 1944.

PRESENT INVESTIGATION

The present group of subjects included 28 patients at the Worcester State Hospital, of whom 11 were male and 17 female. Their ages ranged from 16 to 52 years, the average age being 30. All but 2 patients were given shock therapy, the treatments beginning one to two months after the patient's admission. The 2 exceptions, one of whom had a bromide intoxication and the other a disturbance diagnosed as involutional melancholia, improved so rapidly that no accessory treatment was introduced. The patients were classified as follows: involutional psychosis, 4; bromide intoxication, 1; manic-depressive psychosis, 2; undiagnosed psychosis, 2; psychoneurosis, 3, and schizophrenia of various subtypes, 16.

The general plan of procedure was to make two determinations of the glucose tolerance by the Exton-Rose technic, at an interval of one week; institute the shock therapy and then redetermine the glucose tolerance at monthly intervals after the beginning of the treatments. The number of tests varied, depending on the length of the patient's stay in the hospital, but ranged from three to eight, the



Mean values for glucose tolerance as determined by the Exton-Rose technic for 20 normal subjects and for 28 psychotic patients (before treatment).

In this chart, the values for normal subjects (20) are represented by a solid line and clear circles, the values for psychotic subjects (28), by a broken line with black circles.

average number being six. The period of observation after completion of shock therapy was variable, the usual time being six months. Some of the patients who had left the hospital because of their improved state were retested when they returned for a follow-up visit.

On the day that the glucose tolerance was measured by one of us (H. F.) a psychiatric examination was made by the other (R. Z.). The two examinations were made in complete independence of one another, and the separate results were compared only later.

The glucose tolerances were studied by the Exton-Rose technic, in which three samples of venous blood were taken at half-hour intervals, with the patient in the fasting state. After the first and second specimens of blood were withdrawn, the patient ingested 50 Gm. of glucose dissolved in 275 cc. of water. The blood sugar was processed by the Folin-Wu technic (macroalkaline tartrate) and measured by a photoelectric colorimeter.

The mean values for the glucose tolerance tests for the 28 patients before treatment are shown in the chart. The chart indicates also the mean values obtained for a group of 20 normal men in a previous study.[1b] The normal trend is typically one in which there is a prompt rise in blood sugar within thirty minutes after the ingestion of the first 50 Gm. of glucose. The second dose of glucose is followed in the majority of cases either by no rise or by a fall in blood sugar in the succeeding half-hour. For about one-third the normal subjects there is a secondary rise but the usual trend shown by our group and by normal subjects reported in the literature [5] was that just noted. For the patients the fasting and thirty minute readings were at levels similar to those for the normal subjects. The last reading, however, showed a strong upward trend, quite different from that for the normal subjects and indicative of a decrease in the glucose tolerance. This reduction occurred with all types of psychosis in a larger series of patients, and even in psychoneurotic patients.[1b] In the present series of patients no difference was noted between the values for the male patients and those for the female patients.

The results of treatment were evaluated by one of us (R. Z.); on that basis, the patients were divided into three groups: those who showed great improvement, those who showed moderate improvement and those who showed no improvement (table 1). In general, the first group was able to leave the hospital, whereas the

TABLE 1.—*Mean Values of Glucose Tolerance for 28 Psychotic Subjects Grouped on the Basis of Degree of Improvement Following Shock Therapy*

		Glucose Tolerance, Mg./100 Cc.					
		Control			After Treatment		
Results of Treatment	No. of Patients	Fasting	30 Min.	60 Min.	Fasting	30 Min.	60 Min.
Pronounced improvement	9	97	138	166	101	141	155
Moderate improvement	12	92	133	150	94	130	142
No improvement	7	96	136	168	91	135	165

second group showed a good institutional adjustment. A few patients who showed temporary improvement and later relapsed were included in the third group, with the patients who showed little or no change in their psychotic behavior.

The glucose tolerances obtained on the last occasion on which the patients were examined were used for the "after-treatment" values and were compared with the readings obtained before therapy was instituted. Both before and after treatment the mean values showed abnormal trends, i.e., a lowered sugar tolerance. There is some tendency for this abnormality to be decreased after treatment, as shown by the lower sixty minute levels of blood sugar in the "after-treatment" column, particularly for the patients showing great improvement, but this change is not significant. As a group, then, one cannot say that the clinical status of the patient was correlated to any significant degree with the glucose tolerance.

It is of interest that among the 9 patients who showed pronounced improvement, there were 8 women and only 1 man. In the group with moderate improvement, 7 were women and 5 men. Thus, of the 17 women, 15 showed some degree of improvement, as compared with 6 of the 11 men. This difference in results is probably due to the fact that all but 1 of the men had schizophrenia, while the women included those with involutional and affective disorders, with only 3 who had schizophrenic (catatonic) reactions.

5. Exton, W. G., and Rose, A. R.: The One-Hour, Two-Dose Dextrose Tolerance Test, Am. J. Clin. Path. **4**:381-389, 1934. Matthews, M. E.; Magath, T. B., and Berkson, J.: The One-Hour, Two-Dose Dextrose Tolerance Test (Exton-Rose Procedure), J. A. M. A. **113**:1531-1537 (Oct. 21) 1939.

The relation of the diagnostic grouping to the changes in blood sugar after treatment is shown in table 2, in which the patients are divided on the basis of their psychiatric classification. For the 16 schizophrenic patients, no change in the mean values for the glucose tolerance test is shown after shock therapy. For all the other groups there is some decrease in the one hour values after treatment as compared with the corresponding levels before treatment. Although the numbers of patients in each group and the decrease of blood sugar values are too small to be statistically significant, it is of interest, nevertheless, that the 12 nonschizophrenic patients (whose prognosis was better) showed a greater tendency to normalization of their sugar values than the 16 schizophrenic patients (for whom the prognosis was poor.)

TABLE 2.—*Results of Sugar Tolerance Tests Before and After Treatment According to Diagnostic Groups*

Diagnosis	No. of Patients	Glucose Tolerance, Mg./100 Cc.					
		Before Treatment			After Treatment		
		Fasting	½ Hr.	1 Hr.	Fasting	½ Hr.	1 Hr.
Schizophrenia	16	93	127	148	92	128	147
Involutional psychosis	4	98	143	174	108	137	155
Manic-depressive psychosis	2	92	142	164	104	146	152
Other psychoses	3	99	143	174	100	141	162
Psychoneuroses	3	97	142	184	94	141	163
Normal subjects	20	93	128	117	...	...	...

In an attempt to evaluate correlations and to seek relations in our individual cases, it seemed advisable to set up three groups: (1) cases in which there were psychiatric change, general improvement and a corresponding alteration in the glucose tolerance at some time in the course; (2) cases in which there were psychiatric improvement and no particular change in the glucose tolerance, and (3) cases in which there was no psychiatric improvement and no change in the glucose tolerance.

The first group comprised 12 patients who were diagnostically heterogeneous and included 6 patients with schizophrenia, 2 with involutional psychoses, 2 with psychoneurosis, 1 with manic-depressive psychosis, manic type, and 1 with an undiagnosed psychosis. We have selected several cases to present in some detail to show trends in which psychiatric changes and alterations in glucose tolerance appear to be correlated. The serial tolerances are shown in table 3.

CASE 1.—In this case of reactive depression in a young woman, both recovery and relapse were fairly closely correlated with changes in glucose tolerance. The interviews at the time of the first two tests indicated the presence of depression with retardation and considerable somatic tension (faint tremors; sighing respirations). Coincident with the third test, which showed an improved tolerance, the

TABLE 3.—*Several Sugar Tolerances Before and After Treatment for 8 Patients with Psychotic States*

Case Number and Diagnosis	Glucose Tolerance Ratings, Mg./100 Cc. Before Treatment	After Treatment 30 Min.	After Treatment 60 Min.	Date	Comment
1 Reactive depression	96	172	215	1/30/45	Electric shock 3/15/45 to 4/23/45 (11 treatments)
	91	131	185	2/ 7/45	
	91	121	123	3/14/45	
	96	140	128	4/10/45	
	92	155	115	5/ 9/45	
	102	141	161	6/13/45	
	97	152	145	9/12/45	
2 Manic type	98	168	178	3/28/45	Electric shock 4/5/45 to 4/23/45 (6 treatments)
	91	156	193	4/ 3/45	
	108	179	204	5/ 2/45	
	106	164	194	6/ 6/45	
	103	147	110	9/19/45	
3 Psychoneurosis	108	160	173	11/22/44	Electric shock 6/4/45 to 6/28/45 (8 treatments)
	107	164	182	11/29/44	
	100	149	144	1/10/45	
	103	148	146	3/21/45	
	104	126	172	5/23/45	
	105	152	193	6/27/45	
	104	143	209	9/21/45	
4 Schizophrenia	91	144	154	12/ 5/44	Patient paranoid, irritable, overproductive
	101	156	166	12/13/44	Increased irritability
	96	135	135	1/10/45	Patient irritable, tense; electric shock 12/15/44 to 2/6/45 (16 treatments)
	100	175	232	2/ 7/45	Patient improved; composed; 2 days later, severe relapse
	91	123	118	3/13/45	Patient improved; tense, tearful
	93	130	146	4/24/45	Patient improved but irritable
	90	116	129	9/14/45	Patient improved; less tense and irritable
5 Undiagnosed psychosis	90	142	172	12/27/44	Electric shock 1/15/45 to 2/5/45 (6 treatments)
	91	128	173	1/ 3/45	
	101	135	164	2/ 6/45	
	87	128	152	3/20/45	
	96	148	180	4/25/45	
	95	160	188	6/27/45	
	103	140	172	9/19/45	
6 Schizophrenia	99	134	105	3/28/45	Electric shock 4/5/45 to 6/4/45 (18 treatments)
	84	136	145	4/ 3/45	
	92	159	201	5/ 2/45	
	102	156	205	6/ 6/45	
	106	173	248	6/27/45	
	108	178	219	9/19/45	
7 Bromide intoxication; mixed psychoneurosis	116	158	198	3/13/45	Bromide level, 161 mg/100 cc.; patient fearful, hallucinated
	113	165	203	3/20/45	Bromide level, 127 mg./100 cc.; patient slightly improved
	110	162	187	3/27/45	Bromide level, 105 mg./100 cc.; patient much improved
	102	163	183	4/ 4/45	Patient recovered from psychosis; neurotic
8 Schizophrenia	98	155	181	12/27/44	Mood silly, bland, disorganized
	96	151	187	1/ 2/45	Mood vague, preoccupied, silly
	114	160	215	2/ 6/45	Less preoccupation; electric shock 2/9/45 to 2/13/45 (2 treatments)
	93	130	161	4/10/45	No change; vegetative state
	95	108	140	5/ 2/45	No change; lethargic state
	99	160	170	9/12/45	Some deterioration

patient was still tense and depressed, but less so, and was then able to attend the occupational therapy classes. At the fourth test the depression had cleared. There was no evidence of tension, and she had made a gain in weight of 15 pounds (6.8 Kg.). The situation remained unchanged at the next test; after this, the patient had a relapse, received shock treatment again and made another recovery.

Case 2.—The patient went through a typical manic episode, with practically complete recovery. The glucose tolerance was consistently reduced throughout the course and for some time after superficial clinical recovery. Eventually, about three months after an intervening period of superficial recovery, the glucose tolerance became normal (although, of course, it may have been normal before this time), and the examiner on this occasion had the definite impression that the patient's adjustment was considerably better and her recovery more firmly established. It is thought that the glucose tolerance did not return to a normal range until practically all evidence of a disturbed state had disappeared.

Case 3.—In this case of psychoneurosis in a young woman, the history and behavior on admission led to the diagnosis of hysterical delirium, although in the subsequent course the picture was that of a reactive depression. There was practically spontaneous improvement at the time of the third test, when the patient had been out of the hospital for a week. She remained out of the hospital for four months but was in a difficult social situation. During this period the glucose tolerance remained normal. The patient returned to the hospital with a moderately severe depression, which has become progressively worse, after a transitory improvement brought about by a course of electric shock treatment. It is interesting to note, in connection with the last three tests, that as the depression became severer the glucose tolerance became more abnormal.

Case 4.—The patient had a rigid, fixed, paranoid delusional system concerning his wife. At the interview on Feb. 7, 1945, he appeared to have dropped this delusion and seemed fairly well composed. However, on this date he displayed his most abnormal glucose tolerance. The explanation was fairly evident when, two days later, he had a major relapse, with return of the paranoid system in florid form.

The second group was comprised of 9 patients who showed psychiatric improvement with no particular changes in the glucose tolerance. The diagnostic grouping showed 4 with schizophrenia, 1 with a reactive depression, 1 with manic-depressive psychosis, 1 with involutional psychosis, 1 with bromide intoxication and mixed psychoneurosis and 1 with an undiagnosed psychosis (case 5). This group is important in helping to delineate those factors which are apparently not related to abnormalities in the glucose tolerance. In illustration 2 cases are described in some detail (table 3).

Case 5.—The patient has experienced an almost complete clinical recovery from an acute psychosis, characterized by perplexity, tension, psychomotor retardation, some rigidity and inappropriateness of the affective display, and possibly by auditory hallucinations. Rapid improvement followed six electrically induced convulsions. Her improvement has been maintained up to the present. In contrast, the glucose tolerance curves show only insignificant variations, maintaining their same character throughout the course of the illness.

There are features of this case which may have a bearing on the prolonged impairment of the glucose tolerance. First, several aspects of the symptom picture suggested that the psychosis was a mood disorder (although atypical) and, as

with other patients with mood disorders in our series, the glucose tolerance remained impaired for long periods after recovery from psychotic manifestations. Second, this patient had been "nervous" for a considerable period prior to her psychotic breakdown—this nervousness she described in terms of a periodic disturbance of the vegetative nervous system, with tremors, flushing and feelings of anxiety. She continued to have these episodes and regarded her psychosis as a severe attack of this type.

CASE 6.—For a woman aged 21, with schizophenia, the course of the glucose tolerance values was apparently the reverse of that which might be expected, i.e., on admission the tolerance was normal, and as the course progressed it became abnormal. On admission, the patient was described as being ill at ease and manneristic, with silly, inappropriate affect and a fairly typical schizophrenic thought disorder. After the patient had received electric shock treatment for about one month, the glucose tolerance was found to be grossly impaired. At the same time, a striking change in behavior took place; the patient became overactive and overtalkative, and along with this there was what might be called an erotomania. In effect, the case took on manic features, although the thought disorder persisted. After this phase the patient gradually recovered. At present she is adjusting well outside the hospital and on interview reveals little trace of her psychotic symptoms except for a reluctance to discuss personal matters. This course of events has been most frequent in our patients with mood disorders; for this reason, attention is called to the manic features.

CASE 7.—A tense, anxious woman had a psychoneurosis of long standing. She was admitted to the hospital with an acute psychosis due to ingestion of bromides. Although the bromide level of the blood fell and the psychosis cleared rapidly with treatment, the glucose tolerance remained abnormal throughout the course of therapy, again indicating the absence of relation between acute psychotic manifestations and disturbances in glucose tolerance.

The third group was made up of those patients whose clinical status remained unimproved and whose glucose tolerance curves showed no notable changes. The group comprised 8 patients, 7 with schizophrenia and 1 with involutional psychosis. With respect to the schizophrenic patients in this group, it was felt that, even though they occasionally became more socially adaptable, they remained essentially schizophrenic in their reactions, throughout the period of investigation. In general, while the schizophrenic reaction pattern persisted, they continued to show abnormality in glucose tolerance. There sometimes appeared wide fluctuations in the tolerance curve, the significance of which is not clear; e. g., in case 8 (table 3), the second, third and fourth readings varied widely; yet it was the impression that there was no particular change in the psychiatric status.

COMMENT

Examination of the data in the individual cases reveals the reason for the minor changes in the mean values of the glucose tolerance in the cases in which clinical improvement occurred. In some instances there were striking alterations in the glucose tolerance which paralleled changes in the mental state. In other instances the patient might

improve, whereas the glucose tolerance was unchanged or became even more abnormal. Similar results were obtained by Proctor and associates.[4]

In the majority of cases, the persistent abnormality in the glucose tolerance can be explained by the presence of the residual anxieties which have preceded the onset of the frankly psychotic behavior, and which are not dissipated despite improvement in the clinical picture. The emotional turmoil in such cases is evident in the patient's overt behavior or speech or is demonstrated by the attendant autonomic phenomena, such as hyperhidrosis, tremors or vasomotor disturbances. In a few cases, particularly of schizophrenia, in which blandness of the affect may be a prominent feature, it becomes exceedingly difficult to detect the underlying emotional stress. In such cases, there is a definite need for the use of some such psychologic technic as the Rorschach test, which may uncover this type of disturbance.

It is possible that better correlations might be obtained if the period of observation of the patients were sufficiently long to permit them to work out a more satisfactory solution of their problems. In the present study we have noted that the glucose tolerance tends to become normal in those patients who have acquired some insight into their difficulties. At present we can state only that in the relatively few cases we have studied over a brief period there seems to be evidence of a relation between the findings in the clinical psychiatric examination and the results of the glucose tolerance test.

SUMMARY

A study was made of the possible effect of changes in the mental status on the glucose tolerance (Exton-Rose technic) in 28 patients (11 men and 17 women). The agent used to produce the psychiatric changes was electric shock therapy. A variety of psychotic types were investigated, the commonest classification being schizophrenia (16 cases).

In the majority of cases the glucose tolerance, as a whole, was little affected by the degree of improvement shown, but in individual cases there was a notable relation between the emotional disturbance and the response to sugar. This relation was due not to the presence or absence of psychotic manifestations but to the underlying residue of emotional tension. Only those patients who had apparently made some solution of their problems showed a "normalizing" of their glucose tolerance. It is concluded that the decrease in the glucose tolerance which is commonly seen in psychotic patients is primarily due to the anxiety underlying the mental disturbance.

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CAPILLAROSCOPIC OBSERVATIONS IN CASES OF MULTIPLE SCLEROSIS

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EVIDENCES OF VASCULAR DISORDER IN CASES OF MULTIPLE SCLEROSIS

SINCE the time of Rindfleisch,[1] disturbances in circulation have been described as a part of the histologic picture of multiple sclerosis by the majority of observers. Some pathologists (Ribbert,[2] Borst,[3] Williamson,[4] Klingman[5]) have ascribed an etiologic significance to the alterations observed, and one of us (T. J. P.), with various collaborators, has attempted a systematic survey of the hypothesis that the characteristic lesions are the result of vascular closure. Spotty areas of demyelination, with relative preservation of axis-cylinders and a purely ectodermal type of repair, may be produced by experimental venular obstruction,[6] or may be observed in conjunction with a variety of lesions which embarrass the venous return.[7] Thrombi are observed in or adjacent to the lesions in about 36 per cent of cases.[8] This observation has subsequently been confirmed by Dow and Berglund,[9] who

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9. Dow, R. S., and Berglund, G.: Vascular Pattern of Lesions of Multiple Sclerosis, Arch. Neurol. & Psychiat. **47**:1 (Jan.) 1942.

preferred to neglect the experimental evidence and the histology of lesions produced by venular thrombosis in other diseases, and interpret the thrombi as being the result of demyelination. Scheinker [10] and Marburg [11] accepted the vascular causation of sclerotic plaques. Thrombi are to be seen in other organs of the body in cases of multiple sclerosis.

More recently, disturbances in circulation have been observed in the retina in cases of multiple sclerosis by Benedict [12] and by Brickner and Franklin.[13] In at least some of the cases observed by the latter authors the obstruction appeared to be in the nature of a spasm, which could be relaxed by inhalation of amyl nitrite or other vasodilators.

It seemed reasonable, therefore, to search for alterations in the capillaries in the territory most accessible to direct observation in the living patient, namely, the nail bed. There is, of course, a large literature on the subject of capillaroscopy in diseases of the nervous system, especially arteriosclerosis, Raynaud's disease,[14] thromboangiitis obliterans [15] and epilepsy.[16] Observations in cases of various nerve disorders were made by Marinesco and Bruch.[17] Gomirato [18] made observations in cases of multiple sclerosis. He studied 12 cases and reported dilatation, tortuosity and spiral forms in 80 per cent of them.

PRESENT INVESTIGATION

Material and Methods.—Our observations were made on 48 patients with multiple sclerosis, selected from a larger series on the grounds of certainty of diagnosis, cooperativeness and convenience. For control, 9 persons employed about the laboratory were observed; but, in addition, there is a large series of observations

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17. Marinesco, G., and Bruch, A.: Recherches de capillaroscopie et des troubles vascularies dans quelques maladies nerveuses et des glandes à secretion interne, Presse méd. **38**:665, 1930.

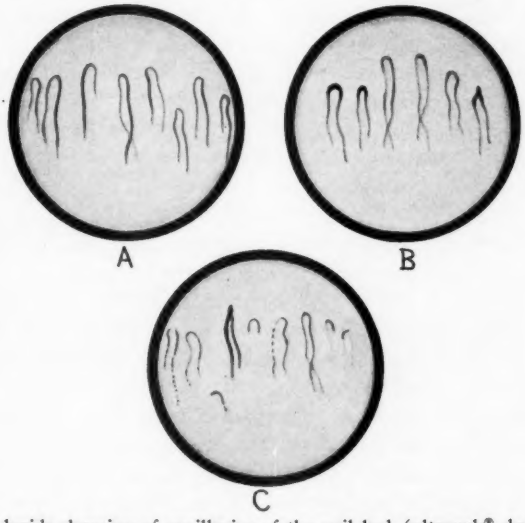
18. Gomirato, G.: Alterazioni dei capillari in malati di sclerosi multipla e loro significato, Riv. di pat. nerv. **53**:148, 1939.

in the literature, which has clearly defined the normal picture (figure, *A*). All subjects, both patients and controls, were between 20 and 45 years of age.

The subject's finger was held firmly in a metal clamp and examined with an ultrapak® dry lens, providing concentric illumination. A green filter was employed. The skin was coated with liquid petrolatum U. S. P. Usually, several fingers of each hand were studied in a subject. The capillaries were always observed at room temperature in a well heated room and before a meal (but never during fasting).

Observations.—The following alterations were observed in cases of multiple sclerosis:

1. Thickening of the intermediate portion of the loop. This abnormality is the most constant. Whether it indicates the formation of a thrombus within the loop is difficult to say (figure, *B*).



Camera lucida drawing of capillaries of the nail bed (ultrapak® dry lens, green filter). *A*, normal capillaries from a control case; *B*, thickening of the intermediate portion of the loop, as seen in 32 of the 48 cases of multiple sclerosis studied; *C*, spasticity and narrowing of the loop, as seen in 36 of the 48 cases.

2. Spasticity and narrowness of greater or less degree, usually more pronounced on the arterial side of the loop. The spasm may reach such a degree that the loop as a whole disappears while under observation, or seems to break up into smaller fragments. Sometimes only the fragments are seen (figure, *C*).

3. Sluggishness or absence of circulation. The blood flow often shows a jerky type of movement, similar to a peristaltic wave. In some capillaries the circulation is slow and discontinuous. The loops are short and thin, as though spastic. The two stems of the loop may be unequal in length. There may be a button-like nodule on the inter-

Abnormalities in Capillary Pattern in the Nail Bed in 48 Cases of Multiple Sclerosis and 9 Control Cases

Case No.	Sex	Size of Loops	Spasticity	Tortuosity	Thickening of Intermediate Position	Fragmentation	Circulation	Engorgement	Comment
1	F	Very small	+++	−	−	+++	−	−	
2	M	Large	+	++	−	−	Jerky	+	
3	F	Short	−	−	−	−	+	−	
4	F	Very short	++	+	++	−	−	−	
5	F	Small	−	−	−	+++	−	−	
6	F	Small	++	−	++	++	+	−	
7	M	Large	++	−	+	+	+	−	
8	M	Large	+	+++	+	−	Jerky and sluggish	−	
9	M	Small	++	+++	+	+	Little	−	
10	M	Normal	++	+	+	−	+	−	Far advanced multiple sclerosis
11	M	Normal	++	−	−	−	+	−	
12	M	Normal	+	−	−	−	Little	−	
13	M	Normal	−	+	−	−	+	−	Normal picture
14	F	Small	++	+	−	++	Slow	−	
15	F	Normal	++	++	+	−	Slow	−	
16	F	?	++	++	+++	+++	Hardly any	−	Heavy smoker
17	F	Small	+++	−	−	+++	−	−	
18	F	Small	+	++	+	−	+	−	
19	F	Thin and long	++	+	+	+	Little	−	Complete remission
20	M	Short	+++	++	−	+++	−	−	Heavy smoker
21	M	Medium	+	+	+	−	−	−	
22	F	Short	++	+++	+++	−	Little	−	
23	M	Large	−	++	+	−	−	+	Poorly visualized, thick cuticles
24	M	Short	++	+	+++	++	Sluggish	−	
25	F	Small	−	+++	+	++	+	−	
26	F	Small	++	+++	−	−	+	−	Complete remission
27	M	Thin	+++	−	+++	−	−	−	Advanced disease
28	F	Variable	++	−	+++	++	−	−	
29	M	Normal	−	+	±	−	+	−	Normal picture; advanced disease
30	M	Normal	+	+	++	++	Sluggish	−	
31	F	Medium	−	+	+	−	−	−	
32	F	Right large	+	++	+	−	−	−	No change after injection of histamine
		Left small	++	−	++				
33	F	Very small	−	−	++	++	−	−	Poorly visualized
34	M	Right very small	−	+	−	−	−	+	
		Left small	++	−	+	..	..	−	
35	M	Normal	++	+++	−	−	+	−	
36	M	Large	+++	−	−	−	+	−	
37	F	Short	−	−	++	−	−	+	
38	F	Large	++	++	−	−	+	−	
39	F	Short—right	−	++	+	−	−	++	
		left	++	+	−	..	Rare	−	
40	F	Very short	++	−	−	++	+	−	
41	F	Right short	−	+	+	−	Rare	−	
		Left longer	..	−	++	..	..	+	
42	F	Large	−	−	+	−	+	−	Almost normal picture
43	F	Short	++	+	+	−	Jerky	−	
44	M	Long	++	−	+	−	+	−	
45	F	Long	−	−	+	−	Slow	+	After glyceryl triacetate: dilatation and good circulation
46	F	Short	++	−	+++	−	Rare and jerky	−	Engorgement after glyceryl triacetate
47	F	Long	+	−	+	−	Jerky	−	No change after glyceryl triacetate; connection with subpapillary plexus
48	F	Right short	−	−	−	−	Rare and jerky	+	Dilatation after glyceryl triacetate
		Left long	+	++	..				
					Control Cases				
1	F	Medium	−	+++	−	++	Little	..	Heavy smoker
2	F	Large	−	+	−	−	+	+	Normal picture
3	M	Large	−	−	−	−	+	..	Normal picture
4	F	Short	−	++	++	−	+	+	
5	M	Medium	−	+	−	−	+	..	Normal picture
6	M	Large	−	+	−	−	+	..	Normal picture
7	M	Large	−	++	−	−	+	+	Normal picture
8	M	Short	−	+	−	−	+	..	Normal picture
9	F	Short	+	+	−	−	+	..	

mediate portion. The distribution of these abnormalities is shown in the accompanying table. In general, women show the changes more clearly than do men.

There seems to be no correlation between the severity or duration of the disease and the alterations in the capillaries. These changes are sometimes severe in early, mild cases with few symptoms, and sometimes inconspicuous in late cases with much disability. They are certainly independent of the degree of paralysis or ataxia of the arm; in none of the cases was the arm severly paretic, and in most instances it was unaffected by the disease. In some cases, one arm was paretic, whereas the other was relatively unaffected; no great difference was found between the two sides.

In presumably normal controls, similar alterations were occasionally seen, but in a much smaller proportion and with less intensity. An apparent exception is the thickening of the intermediate part in 1 control subject. The other changes appeared to be correlated with heavy smoking and with a tendency to vasomotor instability in the control subjects. They usually consisted in various degrees of tortuosity.

COMMENT

As can be seen from the accompanying table, 23, or about 50 per cent, of our 48 cases showed abnormally short and small loops, in close correspondence with Gomirato's figures. In 36, or two thirds of the cases, we found more or less outspoken spasticity, which was also observed by Gomirato in 8 of his 12 cases. Circulation was absent in 5 of his cases and in 14 of ours. Engorged loops were rather rare in our material. The most conspicuous observation was thickening of the intermediate portion of the loop, or button-like nodules on the top, which we saw in 32 cases. (Gomirato described it in only 3.)

In all but 1 of our 9 control cases various degrees of tortuosity of the capillary loops were noted. Spasticity was encountered in 1 instance and thickening of the intermediate part in another. In all of the cases circulation was present.

Vasodilator drugs were tried in 5 cases. Hypodermic injection of 0.5 cc. of histamine produced no apparent change in 1 case. In 4 others $\frac{1}{200}$ grain (0.32 mg.) glyceryl triacetate U. S. P. was given sublingually. In 3 cases the capillaries showed various degrees of dilatation within two or three minutes after administration, whereas in 1 case they appeared unaffected.

In a single case we saw a connection between the capillaries and the subpapillary venous plexus. This is a normal arrangement in infants. If persisting into adult life it is considered by some authors as a developmental defect and has been observed in mentally retarded persons. Our patients did not belong to this group, however.

SUMMARY

Capillaroscopic observations on 48 patients with an established diagnosis of multiple sclerosis are described. Observations on a number of control subjects are also cited for reasons of comparison.

Almost all of the 48 patients (19 men and 29 women) showed definite alteration of the capillaries, consisting mainly in spasticity, sluggishness or absence of circulation and thickening of intermediate parts of the loop.

The capillary findings did not correspond with the severity of the patient's clinical picture.

These observations seem to point to the primary nature of vascular changes in multiple sclerosis.

We think that the presence of abnormalities in capillary pattern in association with neurologic signs and symptoms may prove reliable, though not infallible, evidence in favor of the diagnosis of multiple sclerosis.

These investigations will be continued on a larger scale with respect to the influence of various chemical and physical agents on the capillary shape.

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News and Comment

RESIDENCIES IN NEUROLOGY, VETERANS ADMINISTRATION

Three appointments to residencies in neurology are available at Winter Veterans Administration Hospital, Topeka, Kan. The hospital has been accredited by the American Medical Association for two years of residency training in neurology. During the past three years Winter Veterans Administration Hospital has maintained a residency program in internal medicine and, in collaboration with the Menninger Foundation, an extensive residency program in psychiatry. A residency program in neurosurgery has been applied for. The training program in neurology provides for clinical and didactic instruction, including laboratory training in neuroanatomy, electroencephalography and neuropathology. The number of neurologic admissions per year is approximately 400, and the average number of neurologic patients on the service is 75. Residents in neurology have the opportunity of clinical assignments in neurosurgery and psychiatry. Applications should be sent to the Director of Professional Education, Winter Veterans Administration Hospital, Topeka, Kan.

VETERANS ADMINISTRATION RESIDENCY TRAINING IN NEUROPSYCHIATRY

A limited number of openings are available at this time for appointment on July 1, 1949 to the Veterans Administration residency training program in neuropsychiatry. This program is under the jurisdiction of the deans of the Boston medical schools (Harvard, Tufts, Boston University). Training in this program, which may be from one to three years, is given at the following hospitals:

Cushing Veterans Administration Hospital, Framingham, Mass.
Bedford Veterans Administration Hospital, Bedford, Mass.
The Mental Hygiene Clinic of Boston, Regional Office of Veterans Administration, Boston.
West Roxbury Veterans Administration Hospital, West Roxbury, Mass.
White River Junction Veterans Administration Hospital, White River Junction, Vt.

Emphasis in the entire program is on psychiatry with dynamic orientation and includes closed ward, open ward and outpatient work, child psychiatry and neurology.

All stations are within commuting distance of the Boston Psychoanalytic Institute, in the event that applicants have been accepted for psychoanalytic training.

For information, write to Dr. J. L. Hoffman, Chief of Professional Services, Bedford Veterans Administration Hospital, Bedford, Mass., or to Dr. Wilfred Bloomberg, Chief of Neuropsychiatric Service, Cushing Veterans Administration Hospital, Framingham, Mass.

FELLOWSHIPS OFFERED BY CHILD CENTER, CATHOLIC UNIVERSITY, WASHINGTON, D. C.

The Child Center of the Department of Psychology and Psychiatry, Catholic University, Washington, D. C., announces two fellowships (grants, $2,400 for eleven months) in child psychiatry for physicians who have completed one year of internship and one year of psychiatric training under supervision approved for the American Board of Psychiatry and Neurology.

Further information may be secured from the Medical Director, Robert P. Odenwald, M.D., Child Center, Catholic University.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

THE NEOCORTEX OF HAPALE. JAMES K. PEDEN and GERHARDT VON BONIN, J. Comp. Neurol. **86**:37 (Feb.) 1947.

Peden and von Bonin have studied the cellular structure of the cerebral cortex of a marmoset (Hapale), a very simple primate from South America. One brain was available, from an animal of undetermined species. The brain, after fixation in solution of formaldehyde U. S. P. (1 : 4) for several weeks, was divided into right and left halves. After being embedded in paraffin, the left hemisphere was sectioned crosswise and the right hemisphere lengthwise, in the sagittal plane. Beginning with the first section, every tenth section was stained with cresyl violet; and, beginning with the second section, every tenth section was stained by the silver method of Bodian. To designate the cytoarchitectural areas of the brain, the authors follow the nomenclature used by von Economo in his description of the human cortex. The naming of the areas in Hapale is based on similarities of cell type, cortical lamination and location of areas to those in man, but it is not claimed that the similarly named areas in the marmoset and in man are exactly homologous.

Externally, the brain of Hapale has a simple fissural pattern. There are a well marked lateral fissure and a shallow temporal sulcus. On the medial surface, the calcarine fissure is well defined. It begins near the occipital pole and extends forward, to become continuous with the hippocampal fissure beneath the splenium of the corpus callosum. The sulcus of the corpus callosum, which separates the limbic area from the corpus callosum, is almost as deep as the lateral fissure.

The authors measured the relative thickness of each of the six layers constituting the gray matter of the cortex in 23 areas. Because of the obliquity with which many of the areas were necessarily cut, they made no attempt to measure the absolute thickness of the cortex or of its individual layers. The study represents a phase of the search for an understanding of the basic pattern of the primate brain. The physical features of the animal itself indicate a low position in the primate group. Its behavior in training experiments likewise shows a limited range. However, the occipital lobe shows about as high a degree of differentiation as that of most other primates. Associated with this high development of the visual cortex, Hapale has a well developed macula lutea in its retina and a highly organized lateral geniculate body. The olfactory formations are less extensive than in some other primates and do not reach to the tip of the temporal pole. This preponderance of visual over olfactory development supports the old observation that Hapale relies more on vision than on olfaction in the search for food. Except for the motor cortex, the frontal lobe is differentiated but little. The acoustic cortex of Hapale shows little differentiation. The somesthetic cortex shows almost as poor differentiation as the acoustic cortex. On the frontoparietal operculum is an area comparable to Broca's area in man. This area apparently belongs to the fundamental pattern of the primate cortex. Peden and von Bonin suggest that the precise function of this area deserves to be worked out in greater detail in all primates from Hapale to man. They conclude that differentiation in the cortex of Hapale has proceeded further than the habits and behavior of that animal would suggest.

ADDISON, Philadelphia.

THICK AND THIN FIBERS IN THE PYRAMIDAL TRACT. W. J. C. VERHAART, Acta psychiat. et neurol. **23**:271, 1947.

This study is based on counting fibers and measurement of human pyramids in normal and pathologic brains, the pathologic states consisting chiefly of capsular softenings and related conditions. Twenty-three normal and 10 degenerated human pyramids were studied. Haggqvist's eosin–methylene blue staining technic, which shows both the axons and the myelin sheaths distinctly, and the Whipple square for counting were used, the pyramid always being examined at the midolivary level. Fibers were counted in five groups, the first consisting of fibers about 1 micron in diameter, the others containing fibers 2 to 3, 3 to 5, 5 to 8 and more than 8 microns in thickness.

In the normal pyramids, thin fibers were much more numerous, amounting to about 90 per cent of the total number. Old age did not always cause atrophy. No relation weight of brain, use of pyramidal tracts and number of fibers could be established. The numbers of fibers in the various groups varied considerably. The majority of the very thin fibers were corticofugal. In 2 cases of hyperplasia of a pyramid, as a counterpart to degeneration of the other, only the thick and the medium-sized fibers took part in the hyperplasia. It is probable that the thin fibers arise from a more sensitive cortical area than the thick ones. The premotor cortical area is the site of origin of a great number of thin fibers. Capsular lesions may cause degeneration of large numbers of thin fibers, as well as of thicker ones.

DONALD, Philadelphia.

Physiology and Biochemistry

ELECTROMYOGRAPHIC INTERFERENCE IN THE HUMAN ELECTROENCEPHALOGRAM: A STUDY OF THE EFFECT OF MILD CURARIZATION. DONALD D. MARK, Am. J. Physiol. **149**:538 (June) 1947.

Mark studied the electroencephalograms of 38 subjects before and during curarization to determine whether frontal leads as ordinarily employed pick up muscular as well as cortical activity. He also attempted to determine whether curarization is of value in distinguishing muscular from cortical activity. Electromyographic interference was found to occur in the electroencephalogram in 49 per cent of subjects, the interference occurring especially in the anterior frontal leads. Two thirds of the records with the rapid frequency potentials of muscular origin were improved by curarization in that the muscle artefact was decreased or abolished. Mark concludes that intravenous injection of curare in doses of 0.5 to 1.0 mg. per kilogram may be an adjunct to the interpretation of the electroencephalogram.

FORSTER, Philadelphia.

DISTRIBUTION OF TOTAL ELECTROLYTE, POTASSIUM AND SODIUM IN THE CEREBRAL CORTEX IN RELATION TO EXPERIMENTAL CONVULSIONS. HARRY F. COLFER and HIRAM E. ESSEX, Am. J. Physiol. **150**:27 (July) 1947.

Colfer and Essex studied with microincineration technics the effect of convulsions on the distributions of total electrolyte, potassium and sodium in the cerebral cortex in rats and rabbits. Convulsions were induced electrically, by injection of metrazol® or with sound stimuli. Changes in the cortical neurons were found. After convulsions the cortical neurons showed a diffuse increase of total electrolyte, a loss of potassium and an increase in sodium. These changes were consistent in electrically and chemically induced convulsions but were not

consistent in rats with audiogenic seizures. The shifts in electrolyte were found to have a duration of less than three and one-half hours and were considered to reflect neuronal activity.

FORSTER, Philadelphia.

DECREASE OF PHOSPHOCREATINE IN REGENERATING NEURONS. D. BODIAN and R. C. MELLORS, J. Biol. Chem. **167**:655, 1947.

The changes in motoneurons of the spinal cord of the rhesus monkey after axon section and during the period of regeneration show that (1) the decrease of Nissl substance can be directly correlated with a decrease of cytoplasmic pentose nucleoprotein; (2) acid phosphatase activity is especially increased in the cell body in the region of greatest nucleoprotein turnover, but is also increased in the regenerating axon; (3) cytochrome oxidase and succinic dehydrogenase activity in the cell body is decreased during the period of axon regeneration; (4) resistance to poliomyelitis virus activity is increased during the period of axon regeneration; (5) reflex activity of regenerating neurons is reduced as compared with normal. Analyses of phosphocreatine, acid-hydrolyzable phosphate and inorganic phosphate were carried out in motor columns of the enlargements of the spinal cord in monkeys. The ventral columns, containing the motoneurons, were dissected out of the spinal cord in the frozen state; they weighed about 80 mg. each. The spinal roots corresponding to the left anterior column had been sectioned six or thirty days previously, so that motoneurons on this side were chromatolytic and were regenerating new axons. The right ventral column served as a normal control in each animal. An average decrease of phosphocreatine of about 40 per cent was found in regenerating anterior gray columns as compared with normal gray columns. Adenosine triphosphate values were too low to permit adequate analysis, but combined values of adenosine triphosphate and inorganic phosphate were not significantly different in normal and in regenerating gray matter.

PAGE, Cleveland.

ABORTIVE REGENERATION OF THE TRANSECTED SPINAL CORD. JAMES O. BROWN and GRAYSON P. MCCOUCH, J. Comp. Neurol. **87**:131 (Oct.) 1947.

Brown and McCouch studied the results of complete transection of the spinal cord of 34 cats and 17 dogs. The transections were made between the sixth and the tenth thoracic segment. Various procedures were used to coapt the cut ends of the cord: suturing or not suturing the dura; sealing together the cut ends of the cord with prothrombin, and painting the stumps of the cord with emulsions of degenerated nerve in the hope that products of sheath cells might stimulate growth of axons. In some of the animals small segments of cord were removed and replaced by grafts of nerves taken from other animals of the same species. The character of the transplanted nerves varied—fresh nerves, degenerated nerves, nerves treated with dilute solution of formaldehyde U. S. P. and nerves frozen in vacuo. In some of the experiments on cats, flat tissues, such as omentum, gallbladder, amnion or aorta, were wrapped around the cord. The animals survived from one week to six months. In cases in which spinal standing and stepping had developed to a degree suggesting functional regeneration, the surface of the brain was stimulated with repetitive induction shocks. After death the region of transection was studied histologically by the protein silver (protargol) method for impregnation of nerve fibers.

In none of the living animals did stimulation of the cortex or brain stem induce a detectable response below the section. Histologically, there was observed

in all cases a platelike scar formation across the cord at the site of section. The scar was composed of connective tissue which had grown in from the surrounding injured tissue. At the margin of the scar tissue were regenerating nerve fibers. Evidently, the connective tissue had grown more quickly than the nerve fibers, and the latter had been trapped in the scar tissue. Some of the nerve fibers which had started to grow in had been bent away from their fairly straight course into a transverse position. Other nerve fibers recurved at the side of the scar. The authors conclude that the failure to induce effective regeneration stems, not from lack of growth of axons, but from excess formation of collagenous tissue.

ADDISON, Philadelphia.

PHYSIOLOGIC STUDIES OF ARTERIOVENOUS ANOMALIES. H. A. SHENKIN, E. B. SPITZ, F. C. GRANT and S. S. KETY, J. Neurosurg. **5**:165 (March) 1948.

The authors estimated and analyzed the physiologic changes occurring both in the cerebral and in the general circulation in the presence of a vascular anomaly of the brain. They drew the following conclusions: In an arteriovenous shunt the resistance of the cerebral capillary barrier is eliminated and a considerable increase in blood flow through the affected part results. This decrease in cerebral resistance contributes to a decease in total peripheral resistance and leads to a slight decrease in the blood pressure, most noticeable in the diastolic reading. There is a compensatory enlargement of the heart, with increased cardiac output.

The authors believe that a study of the systemic circulation might be helpful in the diagnosis of a large cerebral arteriovenous anomaly, special attention being paid to an enlarged heart, lower than normal blood pressure, and an increased cardiac output.

TOZER, Philadelphia.

HYPOTHALAMUS AND PITUITARY GLAND. G. W. HARRIS, Brit. M. J. **1**:339 (Feb. 21) 1948.

Harris discusses the relation of the hypothalamus to the pituitary gland and presents evidence that the hypothalamus controls the secretion of both the anterior and the posterior lobe of the pituitary gland. It is suggested that control of the anterior lobe is probably exerted by means of a humoral relay through the hypophysial portal vessels. Neural regulation of the anterior lobe of the pituitary brings indirectly under nervous control the testis, ovary, thyroid and adrenal cortex, via the mediation of the pituitary eutrophic hormones. The activity of the posterior lobe of the pituitary is regulated chiefly by the supraopticohypophysial tract. There is evidence to support the view that this mechanism plays a physiologic part in labor. Harris suggests that, from the results of animal experimentation, in replacement therapy during labor the purified oxytocic fraction be used instead of whole posterior lobe extracts.

ECHOLS, New Orleans.

VARIATIONS OF ARTERIAL PRESSURE DURING COURSE OF CURARE-CONTROLLED ELECTRIC SHOCK THERAPY. L. MASSION-VERNIORY, E. DUMONT, R. NICAISE and H. REINHOLD, J. belge de neurol. et de psychiat. **47**:624 (Oct.) 1947.

The elevation of the arterial blood pressure during the tonic stage of electric shock therapy, and even during the postconvulsive period, is one of the serious contraindications to this treatment. The hypertension associated with electrically produced convulsions in man differs from that in rabbits by the presence in the

former of pronounced increase in intra-abdominal pressure. The authors express the belief that rise in abdominal pressure plays as great a part in elevation of blood pressure as does cerebral excitation. On the contrary, in electrically produced convulsions with the use of curare, the conditions in man approach those in experimental animals, and the intra-abdominal pressure remains approximately normal. Thus, the effect of muscular spasm on the elevation of the blood pressure may be eliminated.

DEJONG, Ann Arbor, Mich.

ELECTROMYOGRAPHIC INVESTIGATION OF THE SEQUALAE OF POLIOMYELITIS. F. ROHMER, C. MARX and F. ISCH, Rev. neurol. **79**:748 (Dec.) 1947.

The authors describe several types of electromyographic activity in the affected muscles of 13 patients with poliomyelitis. With maximal contraction, two main types can be distinguished, "simple" and "intermediate."

A "simple" curve consists of isolated activity of independently functioning, remaining, intact motor units. The authors place "single oscillation" curves under this head. Such curves consist of series of spikes of variably higher amplitudes than those in the "simple" curve, of varying duration and of frequencies from 7 to 96 per second. In a severely paralyzed muscle the frequencies are never over 25 per second.

"Intermediate" curves differ from the normal by their isolated spike activity, which can be designated as "grouped" and sporadic. Spontaneous electrical activity, or "pricking potentials," are found in totally paralyzed muscles or those with "single" or "grouped oscillation" curves.

The authors state that spontaneous electrical activity and "pricking potentials" are due to denervated motor units, "fibrillation" as described by Wedell. The "simple" curve is the result of isolated firing of dispersed intact, remaining motor units, whereas the high spikes of the "single oscillation curve" or the "grouped intermediate" type are apparently due to synchronous firing of different motor units. In favor of this hypothesis is the tendency of the amplitude and duration of the spikes of the single oscillation curves to vary inversely from one examination to another in the same subject. The authors advance the hypothesis that synchronization is as much a result of the physiologic malfunctioning of anterior horn cells, due to impaired nutrition of the motor neuron at the site of the disease process, as of reinnervation of multiple motor units by surviving axons.

LEGAULT, Washington, D. C.

DETERMINATION OF PROTEINS IN CEREBROSPINAL FLUID. RICHARD E. EG. OLOFSSON, HUGO NIHLÉN and SVEN BROHULT, Acta psychiat. et neurol, 1947, supp. 46, p. 94.

The authors discuss four methods of qualitative and quantitative protein analysis in relation to their applicability to study of the proteins of the cerebrospinal fluid. Izikowitz' titration method for fractionated protein determination was used in thirty-six analyses of the total protein, globulin and albumin contents of pathologic lumbar fluids. Duplicate determinations were made. Mean errors were: 2.9 per cent for total protein, 4.5 per cent for globulin and 2.6 per cent for albumin. These values were higher than the mean errors given by Izikowitz from his material of normal lumbar fluids. The authors stated the opinion that more important than these statistically calculated errors was the presence of great variations in the series. In some cases in which duplicate determinations showed good conformity, the value of directly determined albumin considerably exceeded the calculated

value, and sometimes the total protein was lower than that of the albumin. Izikowitz found that the mean error for a single determination of total protein, globulin and albumin did not exceed 1 per cent of the determined value. Furthermore, he found that the sum of the values for albumin and globulin was practically identical with the value for total protein. The authors believe that the repeated precipitations, centrifugings and washings of precipitates constitute the principal source of the errors. In correction of these, they suggest the use of a precipitating salt which contains no ammonium (potassium biphosphate and dibasic potassium phosphate). Thorough cleansing and drying of glass tube apparatus removes traces of the precipitate, which may cause a variation in the values.

Electrophoretic analysis gives a more detailed knowledge of the proteins, especially the globulins. However, it demands relatively large quantities of cerebrospinal fluid and for the present cannot be considered suitable as a clinical method.

The precipitin method, which involves the precipitation of a protein antigen by the homologous antibodies in specially prepared immune serums, has yet to be evaluated completely. However, the impure proteins used in preparing the antiserums loom as a possible source of error.

Protein in the cerebrospinal fluid can also be determined by measurements of the light absorption in the ultraviolet part of the spectrum, analysis being made on the filtrate even if ammonium sulfate is used as a precipitating medium. The disadvantages or complications of this method are as follows: (1) The pure components of the amino acid composition must be known when the mixtures of protein are analyzed, as the maximum of absorption depends on the aromatic amino acids present; (2) the presence of as yet disputed or unknown compounds in pathologic lumbar fluids (e. g., nucleoproteins), changes the maximum of absorption.

DONALD, Philadelphia.

Psychiatry and Psychopathology

PSYCHOPATHIC PERSONALITY AS A GENETICAL CONCEPT. E. T. O. SLATER, J. Ment. Sc. **94**:277 (April) 1948.

Slater calls attention to current disagreement concerning the concept of psychopathic personality. The only common feature in all the different interpretations is a lasting incapacity for social relationships. Some would drop the diagnosis because it disposes to therapeutic fatalism. The author prefers to return to Schneider's original definition of an abnormal person who may suffer from his abnormality or who causes society to suffer. Abnormal, used in Schneider's sense, means only falling beyond the usual, very wide individual range of behavior. In Anglo-Saxon psychiatry illness which makes the patient suffer and illness which makes others suffer have been categorized as entities of a radically different kind—the first neurotic, the second psychopathic, probably because attention has been centered on dynamic factors and diverted from constitutional aspects. Although the psychologic experiences of early life play a part in the etiology of the psychopathic states, hereditary factors have a predisposing role. Clinical experience indicates that the distinction between psychopathic and neurotic reactions is artificial. Both reactions may be present in the same patient at the same time, or the reactions may alternate.

to physiologic causes and that intelligence ratings fall along a normal distribution

It is now fairly well established that variation in intelligence is largely referable

curve. There is every reason to suppose that the same spread holds for temperamental traits. Human beings must be held to vary, in a way which is adequately pictured by the normal curve, in not one but many independent, though correlated, dimensions of personality. Some of these are a general tendency to neuroticism, disposition toward the opposite poles of an affective or hysterical reaction, body type and size, levels of aspiration, and suggestibility. Such traits are closely connected with an inclination to meet environmental stress with neurotic symptoms. Certain personality traits are associated with symptoms of a particular kind. The proximate causes of emotional illness lie in the stresses and strains of life, but the predisposing causes lie in the organization of the brain. By analogy with mental deficiency and the endogenous psychoses, it is proposed that a part of the total variance in temperamental trends is to be accounted for genetically. It is significant that psychopathic personalities found in schizophrenic families are very different from those who are relatives of persons with manic-depressive psychoses. The psychopathies which are linked to the psychoses may, therefore, like the psychoses themselves, be the results of single genes. Childhood cerebral disease may also influence temperament. Profound personality changes are wrought by cerebral trauma; and other organic cause, such as alteration in endocrine balance, is to be considered. There is, finally, the possibility that the constitution, in the practical sense of the term, may be seriously altered by psychologic experiences. The constitution cannot be viewed narrowly, for genetic effects change throughout life as latent genes begin to make their effects felt when brought to the foreground by specific environmental events. There is, for example, a genetic basis for delirious and confusional states. Also, the environment constantly molds and alters the personality and its disposition to special forms of reaction. Such modifications, however, cannot account for the greater part of variation in temperament between persons. There is ample evidence, from the work of geneticists on twins, of the guiding hand of heredity. We do not know whether the effects are the work of one or many genes, but the evidence points to multifactorial inheritance of genes of small effect. Acceptance of the importance of genetic constituents in emotional illness may impose a realistic caution but does not lead to a static conception of personality or deny the possibility of modification by either psychologic or physical therapy.

BEATON, Tucson, Ariz.

HISTAMINE LEVEL OF THE BLOOD IN SCHIZOPHRENIA. T. STRENGERS and J. A. H. GOOZEN, Encephale **10**:283, 1946-1947.

In 1930 Buscaino suggested that histamine intoxication played a large role in the causation of schizophrenia. Jager in 1937, using the Barsoum-Gaddum technic of histamine determinations, flatly contradicted Buscaino. Jager found no evidence of increase of histamine in the blood of schizophrenic persons, and he was unable to see any connection between the metabolic disturbances of schizophrenia and the level of histamine. Strengers and Goozen point out that Jager used 3 normal persons and 12 patients with various disorders. They believe that his normal values for histamine were erroneous.

The authors, in investigations on the importance of histamine in the blood in general and after electric shock treatment, were struck by the evidence of high histamine levels in the blood of schizophrenic patients. Their results were in complete contrast to Jager's. They used Code's modified technic for determination of histamine on 12 schizophrenic patients and, as controls, on 7 other patients with mental deficiency, manic-depressive psychosis and organic psychoses. Their esti-

mate of the average normal histamine value was 6.9 micrograms per hundred cubic centimeters of blood, with a range of from 3 to 12.5 micrograms. Only 3 of the 12 patients with schizophrenia showed normal values, and for these the diagnosis was debatable or doubtful. For 5 others there were increased blood levels (high normal), and for 4 others the levels were very much elevated (19, 21.5 and 29.0 micrograms per hundred cubic centimeters of blood). The values for the control group were all at normal levels. One idiot in the control group showed a very low level of 1 microgram per hundred cubic centimeters. All the schizophrenic patients showed levels higher than 10 micrograms per hundred cubic centimeters. However, the authors are in no way convinced that histamine intoxication plays the major role in schizophrenia. It may be one link in the chain of causation. On the basis of a large series of animal experiments, Strengers could find no correlation between histamine levels and abnormal animal behavior. In a study of asthmatic patients the same lack of correlation was found. The authors feel that there may be a tendency to diminished absorption of histamine by the tissues in schizophrenic patients and this tendency may be a mechanism by which the organism protects itself against the possibility of any intoxication by the increased histamine circulating in the blood. They admit that the whole problem is obscure and that more work, on a larger human material, is needed.

ZINKIN, New York.

PARANOIA OF KLEIST: ENCEPHALOGRAPHIC EVIDENCE. J. DELAY, P. DESCLAUX, G. BOITTELLE and P. MARTY, Encephale **37**:18, 1948.

The authors applied the technic of encephalography to the study of various senile and presenile psychoses. This method of investigation reveals the anatomic state of the cerebrum in nosologically closely allied clinical forms and often reveals similar changes in the brain in clinically artificially isolated disease. There is not always a clearcut line of demarcation between the symptoms of presenile and those of senile psychoses.

Kleist in 1912 differentiated a form of paranoia distinct from the paranoia of Kraepelin. He insisted that it was an independent disease, characterized by four essential features: (1) onset in the presenile period, usually between the ages of 45 to 55, and ten times as frequent in men as in women; (2) delusions of grandeur and persecution of extreme luxuriance, with flight of ideas marked by confabulation and hallucinations, the latter, in 50 per cent of cases; (3) a basic hypoparanoiac prepsychotic personality, and (4) absence of intellectual deterioration. The hallucinations are primarily auditory; visual hallucinations are rare. The delusions are fantastically elaborated and systematized. Affective abnormalities are noted only in connection with the delusional ideas. Kleist carefully separated his disease from Kraepelin's systematized delusions of persecution, prejudice or injury, as well as from the manifestations of cerebral arteriosclerosis.

Albrecht, Halberstadt, Mayer-Gross and Seelert described diseases under various names, which the authors believe are the same as Kleist's paranoia. Jaspers preferred to classify the latter with the schizophrenias. The authors believe that Kleist's description is essentially that of Kraepelin's paraphrenia.

They have been able to study encephalographically about 100 cases of paraphrenia. Their air studies revealed moderate widening of the cortical sulci with normal ventricles, diffuse widening of the sulci with relatively dilated ventricles or isolated dilatation of the ventricles without hypertension of the cerebrospinal fluid. Subsequent neurosurgical intervention or postmortem examination demonstrated the evidence of cortical atrophy.

ZINKIN, New York.

MENTAL DISTURBANCES IN FRIEDREICH'S HEREDITARY ATAXIA. M. BLEULER and H. WALDER, Schweiz. Arch. f. Neurol. u. Psychiat. **58**:44, 1946.

In contrast to the general impression that mental changes are not common in cases of Friedreich's ataxia, Sjögren (*Acta psychiat. et neurol.*, 1943, supp. 27) reported an incidence of progressive dementia amounting to 54 per cent in a group of 74 cases. Bleuler and Walder report the results of psychiatric study of a woman aged 51 who first showed signs of Friedreich's ataxia at the age of 9 years and became bedfast when about 28 years old. This study was undertaken as a matter of scientific interest, since the patient's regular attendants did not consider her psychotic. She was, in fact, a pleasant and cooperative patient. In the course of a penetrating interview, however, it was discovered that she had been experiencing visions of a religious character, as well as auditory hallucinations. Through her suffering she expected to fulfil a divine mission and with the aid of her visions accomplish no less than the ending of the war and the salvation of the world. The prevailing mood was one of euphoria and religious ecstasy. The thinking process was characterized by slowness of reaction, ideational poverty and a strong tendency to perseveration. Comprehension was impaired to some extent, and there was a slight and general failure of memory; events of the remote past were recalled with the same degree of inaccuracy as those of the recent past. Available information indicated that the tendency to exaggerated piety became evident when the patient was about 25 years old. The delusional system seemed to have developed gradually during the past fifteen years.

The authors were impressed by the similarity of mental symptoms in cases of Friedreich's ataxia with those which characterize chronic epileptic psychoses. As a working hypothesis, they suggest that in both conditions cerebral degeneration begins in childhood, progresses at an extremely slow rate and does not attain a high degree of severity.

DANIELS, Denver.

Diseases of the Brain

RETINAL AND CHOROIDAL ARTERIOLES IN MALIGNANT HYPERTENSION. FRANCIS R. MANLOVE, Arch. Int. Med. **78**:419 (Oct.) 1946.

Manlove reports observations on 15 patients with rapidly progressive hypertensive vascular disease. Included in this group were 1 white woman, 1 Negro and 13 white men. Their ages varied from 22 to 65 years. The duration of the disease from the onset of symptoms to death was from five weeks to six or nine months, with an average of sixteen months. One patient had been known to have hypertension for two years but had increased intraocular tension only during the last six months of his illness.

The eyes of 3 of the patients were prepared for sectioning by the pyroxylin method; the eyes of the remaining patients and the control eyes were embedded in paraffin, after the usual fixation with dilute solution of formaldehyde U. S. P. Sections were cut so as to include the nerve head and the macular area. Hematoxylin and eosin, Van Gieson's stain and the elastin H stain were used. In the control series, all the arterioles of both the retina and the choroid appeared normal. No lesions were seen which could be attributed to aging.

From the foregoing material it is evident that in the eyes, as in most other organs, rapidly progressive hypertensive vascular disease was accompanied with pronounced alteration of the structure of the arterioles. Manlove was unable to demonstrate any relation between the arterioles and the other retinal lesions. In fact, several cases in which there were great numbers of retinal hemorrhages and exudates were

remarkable for the absence of any arteriolar disease except a little medial thickening. If the other retinal lesions in the eye in cases of this disease are the result of arteriolar disease, the causal relation remains to be demonstrated.

It is noteworthy that intimal proliferation, seen commonly in the choroidal arterioles, was observed only rarely in the retinal arterioles of Manlove's cases. This may have been due to the fact that the choroidal arterioles observed were, for the most part, of larger caliber than those seen in the retina. However, since such changes were absent even in the largest retinal arterioles, this factor may not be the only one.

Manlove concludes that the wall-lumen ratios of the retinal and choroidal arterioles measured in this series are greater than those of the arterioles measured in any other organ studied by this method except the lung. This observation is in accord with the work of Coats, who stated that the walls of arterioles observed in the eye are thinner than those in other organs. The wall-lumen ratios of arterioles are definitely decreased in cases of rapidly progressive hypertensive disease. The commonest manifestations of arteriolar lesions were medial hypertrophy and intimal proliferation. The choroidal vessels were much more affected than the retinal. Hyalinization of part or all of the arteriolar wall was seen frequently. Acute necrosis was noted occasionally, and no relation was demonstrated between the arteriolar disease and other retinal lesions.

GUTTMAN, Wilkes-Barre, Pa.

TWO TUMORS, MENINGIOMA AND GLIOBLASTOMA MULTIFORME IN ONE PATIENT. EMANUEL H. FEIRING and LEO M. DAVIDOFF, J. Neurosurg. **4**:282 (May) 1947.

Feiring and Davidoff report a case of bilateral frontal lobe tumor, one meningioma and the other glioblastoma multiforme. The patient, aged 58, was admitted to the hospital with the complaint of frontal headache. Operation revealed an encapsulated tumor in the right frontal region, which was entirely removed. Continuous accumulation of fluid under the scalp and evidence of recurrence, namely, increased intracranial pressure, made necessary hospitalization two months later. Reopening of the right craniotomy incision revealed no recurrence of the meningioma. A pneumoencephalogram showed a shift of the ventricular system from left to right, and a third operation was performed, disclosing a glioma-like tumor in the left frontal lobe, which, on section, proved to be a glioblastoma.

TOZER, Philadelphia.

THE PROBLEM OF DISSEMINATED SCLEROSIS. DOUGLAS MCALPINE, Brain **69**:233, 1946.

McAlpine points out that although the cause of disseminated sclerosis is unknown, it seems to lie in the direction either of a biochemical abnormality or of a toxi-infective process. The knowledge derived from certain forms of encephalitis and encephalomyelitis in man and in animals and the part played by viruses suggests that disseminated sclerosis is also infective in origin, particularly when viewed against the histologic background of multiple sclerosis. With this in mind, McAlpine undertook clinical studies to ascertain whether there were factors in favor of, or opposed to, the possible infective origin of disseminated sclerosis. He found no clinical factors contrary to the possibility of, and some in favor of, an infective origin. In analyzing his series of 142 cases, McAlpine found a greater incidence in women. Social standing, occupation and rural or urban existence were of no significance. There was no seasonal incidence for onset of the disease. In 5 per cent of McAlpine's cases there was a familial incidence, which he concluded

indicates a familial predisposition, comparable to that of tuberculosis. There was no distinctive type of body build or coloring, although obesity seemed to offer some protection against the disease. An occasional relation existed between psychic trauma and the onset. In approximately 6 per cent of the cases there was a history of allergy; in general, the patients were in good general health when first attacked by disseminated sclerosis, but in a minority a subnormal state of health or nutrition may have lowered resistance. In 5 per cent of the series trauma had occurred within one month prior to the onset of the disease. In 5 per cent of the cases "influenza" occurred within a month prior to the onset of the disease, and in 2.5 per cent there had been a cold or sore throat without fever. In 13 per cent of the cases peripheral sepsis occurred within one year of the onset, and in one half of these cases the first clinical sign of disseminated sclerosis appeared at approximately the same segmental level.

McAlpine concludes that there are no factors disproving an infective origin for disseminated sclerosis, and some of the factors are evidence in favor of such an etiologic agent. He suggests the possibility that invasion of the nervous system and the appearance of the first clinical signs may not coincide in time, and in that respect may be analogous to syphilis of the central nervous system.

FORSTER, Philadelphia.

CYSTICERCOSIS CEREBRI MISTAKEN FOR CEREBRAL SYPHILIS. A. A. WILLIAMS, Lancet **2**:144 (July 24) 1948.

Williams reports the case of a man aged 29 who had been a soldier in India for seven years and who came to the hospital because of repeated epileptic attacks. He had been discharged from the army because of these fits, which were attributed to cerebral syphilis.

He had slurring speech, some mental dulness and bilateral early optic nerve atrophy. The serologic reactions of the blood were negative. The Wassermann reaction of the cerebrospinal fluid was negative, and the Lange colloidal gold test gave a paretic curve. The patient was given three courses of bismuth therapy, and penicillin and malarial therapy were started, but he refused to continue the latter treatment. The epileptic attacks continued and could not be controlled with drugs. On several occasions he was admitted to the hospital in status epilepticus. On one hospitalization he had an epileptiform attack localized to the right angle of the mouth. During this period weakness of the muscles supplied by the right facial and right spinal accessory nerves developed. The possibility of cysticercosis cerebri was considered, but no nodules were discovered by palpation in any part of the body. He was admitted in status epilepticus, which was uncontrollable, and he died. Autopsy revealed that the brain was studded with numbers of cysts in various stages of development. The typical scolex was demonstrated histologically. A search of the muscles revealed no ova.

The diagnosis is made difficult by the facts that unless the cysts are calcified they cannot be seen in the roentgenogram and that both the eosinophilia and reaction to the complement fixation tests are unreliable. A further difficulty in this case was the presence of optic nerve atrophy, which is unusual with cysticercosis.

MADOW, Philadelphia.

LONG STANDING HYPOPITUITARISM WITH RECENT SIGNS SUGGESTING EITHER CHROMOPHILIC ADENOMA OR SUPRASELLAR TUMOR. H. S. LEMARQUAND, Proc. Roy. Soc. Med. **40**:152 (Feb.) 1947.

LeMarquand reports the case of a woman aged 28 with a history of normal birth and development up to the age of 8 years, at which time diabetes insipidus

occurred, with a spontaneous remission at the age of 11 years. At the age of 20 she had the head size of a 6 year old child, with the weight and height of an 11 and an 11½ year old child, respectively. There were retarded epiphysial development, amenorrhea and undeveloped breasts. With endocrine treatment there was some development of secondary sex characteristics. At the age of 28 the patient complained of diminished vision on the right and showed slight constriction of the right visual field and pallor of the right disk. The pituitary fossa (eight years before reported to be in the upper limits of normal) showed enlargement and thinning of the posterior clinoid processes. Roentgen therapy was instituted, but definite atrophy of the right eye and a right hemianoptic scotoma were present and increasing five months after the first visual disturbance was noted.

BERRY, Philadelphia.

APRAXIA AND DYSARTHRIA IN A CHILD. P. LIESSENS, J. belge de neurol. et de psychiat. **47**:637 (Oct.) 1947.

Liessens reports the case of a child aged 7 years who showed symptoms of motor apraxia, dysarthria and dyspnea. Motor power was normal, but there was difficulty in carrying out skilled movements. Cerebellar functions were normal. Speech was affected in both rhythm and quality. There was marked retardation of intellectual development. The author expresses the belief that the speech defect, as well as the motor anomalies, resulted from inadequate psychomotor control.

DEJONG, Ann Arbor, Mich.

CLINICAL-STATISTICAL STUDIES OF TUMORS OF THE CEREBELLOPONTILE ANGLE. ALFREDO GIVRE, Arch. neurocir. **2**:97, 1945.

Givre analyzes 42 cases (21 patients were male and 21 female) of cerebellopontile angle. In 22 cases the tumor was on the right side and in 20 cases on the left. There were 22 cases of acoustic neuroma, 1 case of meningioma, 1 case of tuberculoma, 5 cases of metastatic tumor, 2 cases of glioma and 2 cases of arachnoiditis. The duration of symptoms varied from twenty days to twenty-five years. In 37 per cent the patients were seen during the first year of illness. In 16 cases (38 per cent) the onset was with acoustic or vestibular symptoms, in 2 with cochlear symptoms and in 2 with vertigo. In 12 of the 16 cases in which onset was with vestibular or cochlear symptoms and in 13 of the 22 cases in which these symptoms were not present the tumor was an acoustic neuroma. No cochlear or vestibular symptoms were present at the time of onset in any of the cases in which the tumor was not acoustic neuroma. The ages varied from 13 to 67 years; two thirds of the patients were between 30 and 50, and 33 per cent, between 40 and 50 years of age. Papilledema was found in 25 of the 42 cases; in 3 cases there was edema with secondary optic nerve atrophy, and in 7 cases there was atrophy without edema. In 1 case, part of one disk was atrophic, with edema in the other part. The author comments on the number of cases in which no choking was seen, owing to early diagnosis of the lesion. Visual acuity was impaired in 24 cases; the fields were altered in 35 per cent. Ocular palsies were seen in 54 per cent of the cases, and there was impairment of the intrinsic musculature of the eye in 14 cases.

N. SAVITSKY, New York.

Book Reviews

Telepathy and Medical Psychology. By Jan Ehrenwald, M.D. Price, $3. Pp. 212. New York: W. W. Norton and Company, Inc., 1948.

From a broad background of psychiatric experience and much critical observation of so-called telepathic and psychic phenomena, Dr. Ehrenwald has written a book that is bound to stimulate discussion. Building on Rhine's statistical findings and his own intensive study of telepathic persons, he describes the telepathic process as "perception by one person of another person's mental processes." He by no means considers telepathic power to be evidence of a supernormal ability; on the contrary, he conceives of it as compensation for a "minus function" in the personality and the real basis of the delusions of paranoid schizophrenia. He modestly calls his own bridging of the gap between telepathy and the psychoses a hypothesis, but he accepts as valid and proved: (1) the "existence of paranormal cognition as an indisputable bedrock truth"; (2) Freud's pronouncements regarding the id, ego and superego, as well as the unconscious, preconscious and subconscious; (3) the doctrine of compensation in the physiology of the senses (hyperesthesia of hearing and touch in the blind), and (4) Kretschmer's theories of types (he would add one of his own: the psychic). In the opinion of this skeptical reviewer, brougnt up on the law of parsimony, if Dr. Ehrenwald should shift his discussion from the telepathic process to the telepathic experience (the mystic feeling of certainty which shades off sometimes to the wistful "there *must* be something to it"), he would be on very solid ground, indeed, in tying in this experience with the fantasy in schizophrenia. His hypothesis, then, that all these experiences serve as compensation for a "minus function" would be a real contribution.

The Treasury of Human Inheritance: Volume 4: Part 5. Dystrophia Myotonica and Allied Diseases, with Clinical Notes by J. Purdon Martin. By Julia Bell, M.A. Price, 21s. Pp. 410, with plates. London: Cambridge University Press, 1947.

Volume 4 of this monumental English work, "The Treasury of Human Inheritance," edited by L. S. Penrose, M.D., is devoted to "Nervous Diseases and Muscular Dystrophies." Part 5 of this volume deals with myotonia congenita and dystrophia myotonica. There is a brief clinical sketch on both diseases. Among the topics discussed are age of onset of the disease, fertility in diseased families, cataract, inheritance and relationship between myotonia congenita and Thomsen's disease. The most valuable part of the work is the pedigrees in 223 cases of myotonia and paramyotonia. These pedigrees have been compiled with the greatest possible detail and thoroughness. This work is by far the most profound study of the genetic basis of myotonia published anywhere—at any time. For years to come, it will be the standard work on this subject. The chronologic bibliography is by no means complete. Many an important publication in English, French or German—even those which contain family trees—is missing. Inaccessibility during the war years cannot be blamed for this, since some of the missing publications have appeared in *The Journal of the American Medical Association* and in these ARCHIVES—for instance, the article of Jelliffe and Ziegler, 1933 (Thomsen's Disease [Myotonia Congenita]: Report of Case and Review of American Literature, J. A. M. A. **100**:555 [Feb. 25] 1933), which contains a review of the American literature on myotonia, is "conspicuous by its absence."

Failures in Psychiatric Treatment. Edited by Paul H. Hoch. Pp. 241. New York: Grune & Stratton, Inc., 1948.

"As an outsider, may I say that I like the emphasis on 'failure' in the topic of this symposium? It is a semantic device beautifully designed to bring down the professional defenses of the therapeutist. It even invites a certain amount of professional masochism. I would like to congratulate the program committee for devising and selecting this title."

J. McV. Hunt thus opens his discussion on one of the topics presented in this interesting proceedings of the thirty-seventh annual meeting of the American Psychopathological Association. It could not be improved on. It is the reverse expression of the time-honored wisecrack that doctors bury their mistakes.

It is remarkable to note the way in which those who participated in the symposium have responded to the call of duty. Acknowledgment of failure is difficult, even when it is called for by the program committee and by the title of the symposium. Indeed, interspersed here and there among the cases of failure reported are many instances of success. One assumes that they represent previous failures but that in the correct treatment they were admitted to the more numerous category of successes.

Perhaps the most forthright author (Merritt) summarizes his discussion by saying: "The primary failure in the treatment of epilepsy is that of the medical profession in its failure to discover the cause of the disease. This lack of knowledge is not, however, an excuse for the failure effectively to use the drugs which are now available for the prevention of seizures. The majority of the failures in the use of these drugs is due to inadequate dosage or improper choice of drug."

Other short chapters deal with failures of psychoanalysis, psychobiology, hypnosis, insulin shock, electric shock and prefrontal lobotomy in the therapy of sick persons. Special difficulties are recorded in the treatment of children, of criminals, of neurosyphilis and of constitutional disorders. Group therapy and social case work and their failures are introduced to round out the picture. As Hoch states in his foreword: "The present symposium is, to our knowledge, the first attempt to present a general review of therapeutic failures with different psychiatric methods of treatment. It is obvious that successful cases are easy to report and the hesitancy to do similarly with unsuccessful ones is understandable. But to admit failures is a sign of intellectual and emotional maturity."

Les discopathies cervicales. By A. Richard, P.-F Girard and P. Dupasquier. Pp. 110. Lyons, France: Dugas, 1948.

This small monograph is an excellent account of disease of the cervical intervertebral disks, based on personal experience with 50 cases, brief histories of which are given. The authors give a brief account of the history of this subject, followed by a study of the normal and pathologic anatomy of the disks, the pathogenesis and etiology of diseases of these structures, clinical and roentgenologic findings, the principal clinical modalities, diagnosis and treatment.

They suggest that the term "herniated disk" be replaced by that of *discopathie*, since the usual lesion is a necrotic degenerative process of the intervertebral cartilage. This lesion, which may be of traumatic, infectious or abiotrophic origin, may have one of two immediate effects, partial or total collapse of the disk, resulting in its protrusion or the dislocation of the chain of vertebral bodies. The secondary results are compression either of the spinal cord or of the cervical spinal roots. These secondary symptoms, whether transitory or permanent, are produced when

some unusual strain or movement exaggerates the herniation or dislocation. The traumatism then sets up an inflammatory reaction in the cord or nerve roots. The interspaces most often affected are those between the sixth and the seventh cervical vertebra and the seventh cervical and the first thoracic vertebra.

The symptoms assume four forms: (1) cervicobrachial neuralgia; (2) amyotrophy; (3) reflex forms, such as torticollis, and (4) vague painful syndromes, known variously as sympathetic aeroparesthesia, pseudoangina and cenesthopathy.

The authors are of the opinion that little help in the diagnosis is to be obtained by lumbar puncture, even by injection of iodized oil U. S. P. They depend mainly on the history and the clinical and roentgenographic findings.

The results of operative treatment are not nearly so good as those for disease of the lumbar disks, and posterior radicotomy is advisable. Medical and orthopedic treatment should always be given a thorough trial.

The authors indulge in much speculation concerning the mechanism of production of the so-called sympathetic syndromes; the subject remains obscure.

This simple, logical, judicious discussion is recommended to all physicians who must care for these difficult and painful lesions.

Fiat Review of German Science 1939-1946. Neurology, Part 1. G. Schaltenbrand, senior author. Pp. 150. **Psychiatry.** E. Kretschmer, senior author. Pp. 300. Office of Military Government for Germany, 1948.

The volume on neurology, the first of three, briefly reviews work done in Germany from 1939 to 1946 on the following subjects: brain research in general, histology of the central and peripheral nervous system, reflexes, hypothalamus, extrapyramidal nervous system and cerebral cortex. The senior author, Schaltenbrand, is well known in the United States through his collaboration with Bailey, Cobb and Putnam. In his preface, he points out the unfavorable conditions under which German neurologists worked in those years. He rightly says that neurology suffered from the fusion with psychiatry which was forced on it by the government in 1935. Despite this, the accomplishments of German neurology are remarkable. In this review they are well covered. The single reviews are sometimes too short. This book will be of great interest to every neurologist. No one who works in any of the fields which are reviewed can afford to pass by the work Germany did from 1939 to 1946.

The review on psychiatry is edited by E. Kretschmer, of "Physique and Character" fame, now professor of psychiatry of the University of Tübingen. The whole field of psychiatric research in Germany from 1939 to 1946 is covered here, including serology, somatic therapy and psychiatry in air force medicine. Problems of constitution and heredity are stressed. The whole study is most interesting and stimulating. The detailed bibliography is useful.

Unfortunately, both works are written in German; only the table of contents and the foreword appear in French and English. It would be much better if it were the other way around. The German-speaking neurologist has easy access to the German literature of the war years. It is the English-speaking neurologist who wants and needs such a review, written in English.